Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Dorman SE, Nahid P, Kurbatova EV, et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. N Engl J Med 2021;384:1705-18. DOI: 10.1056/NEJMoa2033400

Supplementary Appendix

Supplement to: Dorman SE, Nahid P, Kurbatova E, et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis

CONTENTS

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2 Detailed Methods

2.1 Participant inclusion and exclusion criteria for S31/A5349

2.1.1 Inclusion criteria

Individuals must meet all of the following inclusion criteria in order to participate in this study:

A. Suspected pulmonary tuberculosis plus one or both of the following: a) at least one sputum specimen positive (any grade, including scanty) for acid-fast bacilli on smear microscopy OR b) at least one sputum specimen positive for *M. tuberculosis* by Xpert MTB/RIF testing, with semiquantitative result of 'medium' or 'high' and rifamycin resistance not detected.
B. Age twelve years or older
C. A verifiable address or residence location that is readily accessible for visiting, and willingness to inform the study team of any change of address during the treatment and follow-up period.
D. Women of child-bearing potential who are not surgically sterilized must agree to practice an adequate method of contraception (barrier method or non-hormonal intrauterine device) or abstain from heterosexual intercourse during study drug treatment.
E. Documentation of HIV infection status.
F. For HIV-positive individuals, CD4 T cell count greater than or equal to 100 cells/mm^3 based on testing performed at or within 30 days prior to study entry. HIV-positive individuals will be enrolled in a staged approach:
    - Group 1 ("EFV1"): receipt of efavirenz-based antiretroviral therapy (ART) for a minimum of 30 days at the time of enrollment AND a documented HIV viral load less than 200 copies/mL at or within 30 days prior to study entry, OR
    - Group 2 ("EFV2"): for HIV-positive individuals not on ART at enrollment, planned initiation of efavirenz-based ART before or at study week 8
G. Laboratory parameters done at or within 14 days prior to screening:
    - Serum or plasma alanine aminotransferase (ALT) less than or equal to 3 times the upper limit of normal
    - Serum or plasma total bilirubin less than or equal to 2.5 times the upper limit of normal
    - Serum or plasma creatinine level less than or equal to 2 times the upper limit of normal
    - Serum or plasma potassium level greater than or equal to 3.5 meq/L
    - Hemoglobin level of 7.0 g/dL or greater
    - Platelet count of 100,000/mm^3 or greater
H. For all women who are not surgically sterilized or who do not meet the study definition of post-menopausal, a negative pregnancy test at or within seven days prior to screening
I. Karnofsky score greater than or equal to 60
J. Written informed consent.

2.1.2 Criteria for exclusion from enrollment

An individual meeting any of the following exclusion criteria at the time of enrollment or initiation of study drugs will be excluded from study participation:

A. Pregnant or breast-feeding
B. Unable to take oral medications
C. Previously enrolled in this study
D. Received any investigational drug in the past 3 months
E. More than five days of treatment directed against active tuberculosis within 6 months preceding initiation of study drugs
F. More than five days of systemic treatment with any one or more of the following drugs within 30 days preceding initiation of study drugs: isoniazid, rifampin, rifabutin, rifapentine, ethambutol, pyrazinamide, kanamycin, amikacin, streptomycin, capreomycin, moxifloxacin, levofloxacin, gatifloxacin, ofloxacin, ciprofloxacin, other fluoroquinolones, ethionamide, prothionamide, cycloserine, terizidone, para-aminosalicylic acid, linezolid, clofazimine, delamanid or bedaquiline
G. Known history of prolonged QT syndrome
H. Suspected or documented tuberculosis involving the central nervous system and/or bones and/or joints, and/or miliary tuberculosis and/or pericardial tuberculosis
I. Current or planned use within six months following enrollment of one or more of the following medications: HIV protease inhibitors, HIV integrase inhibitors, HIV entry and fusion inhibitors, HIV non-nucleoside reverse transcriptase inhibitors other than efavirenz; quinidine, procainamide, amiodarone, sotalol, disopyramide, ziprasidone, or terfenadine.
J. Weight less than 40.0 kg
K. Known allergy or intolerance to any of the study medications
L. Individuals will be excluded from enrollment if, at the time of enrollment, their *M. tuberculosis* isolate is already known to be resistant to any one or more of the following: rifampin, isoniazid, pyrazinamide, ethambutol, or fluoroquinolones.
M. Other medical conditions, that, in the investigator's judgment, make study participation not in the individual's best interest.
N. Current or planned incarceration or other involuntary detention.

2.2 Sample size considerations

The primary objective of the trial is to evaluate whether rifapentine containing regimens can produce outcomes at least as favorable as standard therapy, but with a shorter treatment course. Therefore, the trial is structured as a non-inferiority study.

Key assumptions:

- Primary endpoint rate: 15% absence of cure (unfavorable) in the standard regimen arm (Microbiologically Eligible population). This rate is based on observed results for the control arm (MITT analysis group) in two recently completed phase 3 clinical trials (27/161 [14%] in the Rifaquin trial and 100/743 [13.5%] at 18 months post

randomization and 114/679 [16.8%] at 24 months after the end of treatment in the Oflotub trial.)

- Margin to define inferiority: 6.6% ($\delta = 0.066$)
- 95% confidence (type 1 error, $\alpha = 0.05$). The sequential testing of regimen 3 and regimen 2 protects the type 1 error rate, as follows: If the statistical test for regimen 3 fails at 95% confidence, then conclude that both experimental regimens are not noninferior. If and only if regimen 3 is noninferior, then proceed to test regimen 2 at 95% confidence. A type 1 error occurs if either regimen is incorrectly deemed noninferior; the sequential approach limits the probability of this error to 5% overall.
- Power: 80% (type 2 error, $\beta = 0.20$) for primary analysis among Microbiologically Eligible subgroup, with power recalculated for the restriction to Assessable subgroup (see below)
- Proportion of enrolled participants who would be found to be late exclusions due to microbiological ineligibility – 12% (based on observed results in recent TBTC phase 2 studies)
- Proportion of enrolled participants who would be found to be 'not assessable': 12% (based on observed results in the Rifaquin trial)

With 816 per arm, we expect 612 assessable. With the expected 15% unfavorable outcomes among those who are assessable, then with the same noninferiority margin and type 1 error rate, we have 90% power to test the primary hypotheses among the Assessable subgroup.

2.3 Justification for Margin of non-inferiority

The 6.6% margin to define inferiority (6.6%) takes into consideration the following issues:

1. the rates in historical trials of inpatient TB treatment for 6-month and 4-month regimens conducted by the British Medical Research Council support a difference in relapse up to 6% (East African/British Medical Research Council 1976, 1977, 1981; East and Central Africa/British Medical Research Council 1986; Singapore Tuberculosis Service/British Medical Research Council 1986; Nunn and Crook 2013);
2. recent trials in contemporary outpatient populations suggest a higher baseline proportion (15%) of unfavorable outcomes likely to be observed based on phase 3 trials and definitions;
3. the investigators in this trial and others perceive that the benefits of reducing treatment duration to 3 or 4 months would have advantages not outweighed by a possible increase in the relapse rate of up to 6%; and
4. the 6.6% margin does not imply that the experimental regimen may result in as much as 6.6% more unfavorable outcomes, but rather, for a fixed design, the maximum difference consistent with a non-inferior conclusion decreases as the proportion of unfavorable outcomes in the control arm increases.

A 6% margin of non-inferiority trials has been used in other recent trials of single-drug substitution treatment shortening trials (e.g. REMoxTB). The justification of this margin is

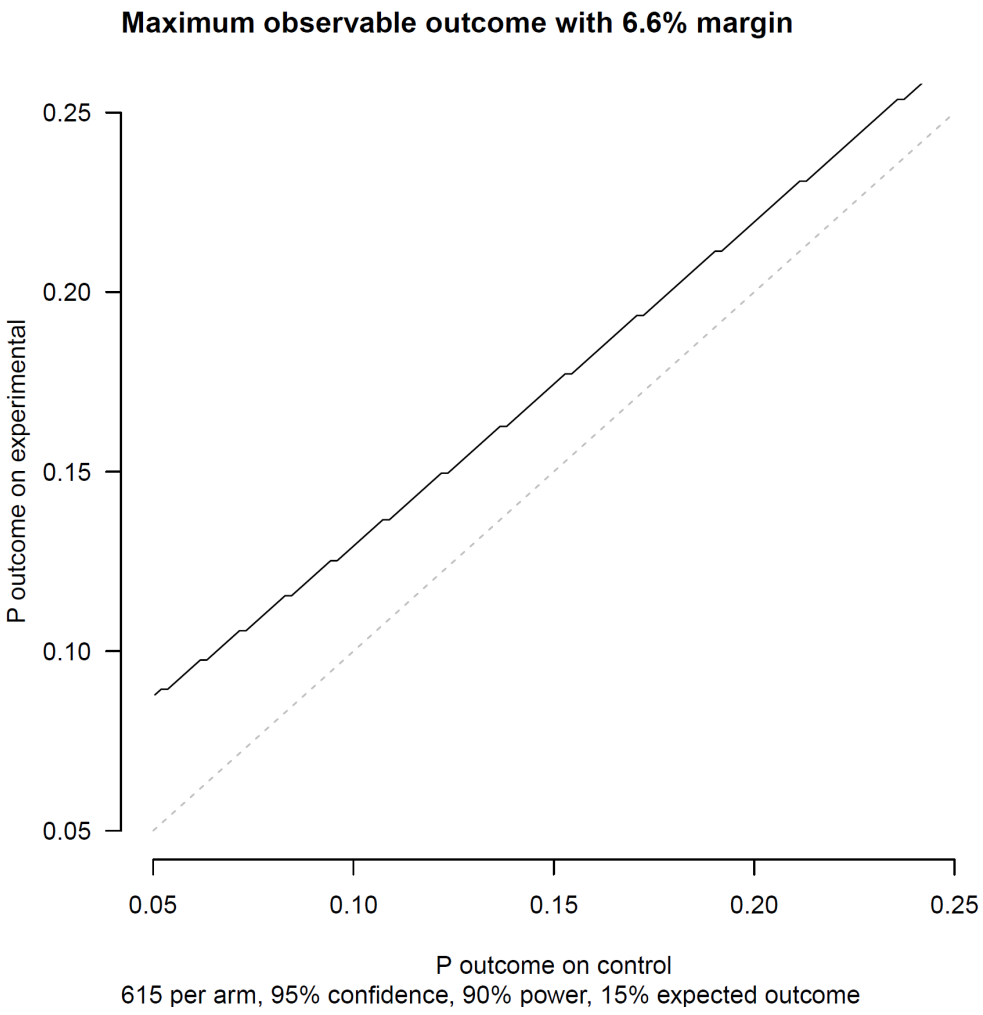
published in the online supplements with these papers (Gillespie et al, 2014 NEJM). We have attached the justification from that study as an attachment to support a 6% margin.

We believe an extension from 6% to 6.6% is justified for the following reasons:

1) The justification for a 4.8% margin in the FDA Guidance for Industry for Pulmonary Tuberculosis Trials is based on previous trials under 'per protocol' type analyses with many post-randomization exclusions, in a largely in-patient population; we observe larger proportions of unfavorable outcomes today than was seen in these relapse-only analyses from previous trials. We feel this provides a justification for a larger margin than 4.8%, and also the 6% that was justified for the REMoxTB trial. Recent trials in contemporary outpatient populations suggest a higher proportion (16% in REMoxTB MITT) of unfavorable outcomes, even than that anticipated in the REMoxTB trial sample size calculations (10%).
   Furthermore, the rationale for a 4.8% margin is based on the situation where a single drug that has an unknown contribution to the regimen is replaced by a new drug (the replacement of ethambutol, for example). In our study, rifampicin is replaced by rifapentine (in addition to the substitution of moxifloxacin for ethambutol in one arm). It is known that rifampicin is the most important drug in the current regimen. It might therefore be appropriate to consider not just the removal of the final two months of therapy (following the argument in lines 829-832 in the FDA Guidance) to estimate M_1, but also the consider the removal of rifampicin from the regimen. This would require consideration of a comparison of six months of HRZE (2HRZE/4HR) with four months of HZE (2HZE/2H) when estimating M_1. We are not aware of any trials that evaluated a 4-month regimen without rifampicin, so providing a comprehensive rationale similar to that which underpins the 4.8% would be challenging but would lead to a larger M_1 and therefore support a margin of non-inferiority larger than 4.8%.

2) Considering the clinical argument (from FDA Guidance and Nunn, Phillips, Gillespie 2008) we, and in broader consultation within our two large publicly-funded international consortia of TB stakeholders (CDC TB Trials Consortium and NIH AIDS Clinical Trials Group), consider the benefits of a 4-month rifapentine-based regimen justify the margin of 6.6%. Our consortia consider 600 patients per arm sufficiently large to provide adequate precision on the difference in efficacy between the regimens to determine whether an intervention regimen might be considered not inferior to the control regimen.

The following graph was used to describe the maximum observable difference (solid line) from in the point estimate from the line of equality (plotted as dashed line) with a 6.6% margin under the stated assumptions.



The FDA Guidance for Industry Pulmonary Tuberculosis: Developing Drugs for Treatment identifies two studies comparing four and six months of TB therapy that provide data to estimate M1 for providing a rationale for the margin of non-inferiority. Study 2 (data from the 4th and 5th EA/BMRC trials) also included two four-month regimens without a rifamycin in the continuation phase, 2SHRZ/2HZ and 2SHRZ/2H. The combined relapse rate in these two arms was 63 (31%) / 203. Using the figures quoted in the FDA guidance document for the 2SHRZ/4HR regimen from this study (4.7% (8/172)), the treatment effect (4-month regimen minus 6-month regimen) is 26.4%, 95% CI (19.3%, 33.5%) for the unstratified risk difference. This lower bound of 19.3% provides an estimate of M1 for the removal of the final 2 months of HR therapy, and the removal of R in months 3 and 4. We want to preserve a reasonable proportion of this treatment effect and have therefore selected a 6.6% margin of non-inferiority which preserves more than 50% of M1.

For these reasons it is our perspective that a margin of 6.6% is justified.

2.4 Definitions for primary outcome status

2.4.1 Definition of primary outcome

Each participant will be classified into one of the following three outcome categories:

1. Absence of Cure (Unfavorable Outcome)
2. Cure (Favorable Outcome), or
3. Not assessable.

The primary outcome is defined as twelve months after study treatment assignment. Actual visit dates, rather than scheduled visit names (e.g. Week 26, or Month 9), will be used for all analyses. See the Statistical Analysis Plan (SAP) section 4.5 for visit windows that define the time periods. In particular, Month 12 includes data from visits up to 442 days from treatment initiation.

Only data up to the end of the Month 12 analysis visit window will be included in the primary analysis of the primary efficacy outcome.

2.4.2 Absence of Cure (Unfavorable)

A participant will be classified as having an unfavorable outcome if any one of the following conditions is met:

1. A participant will be considered to have absence of bacteriological cure if he/she has a sputum sample, obtained at or after Week 17 and no later than the end of the Month 12 analysis visit window, that is Mtb Culture Positive (see SAP section 4.7 for definitions of culture results) that is indistinguishable from the initial isolate (see separate sequencing plan for definitions), and this is confirmed by a second sample that is Mtb culture positive. A second confirmatory sample, on a different day without an intervening Mtb Negative culture result, is required, as a single positive sputum culture result in isolation will not be considered absence of bacteriological cure. If results from strain analysis are inconclusive or unavailable, it will be assumed that strains were indistinguishable.
2. Participants who die from any cause during study treatment ('study treatment phase' is defined in SAP section 4.6), except from violent or accidental cause (e.g. road traffic accident). Suicide during study treatment will be classified as an unfavorable outcome.
3. Participants who are withdrawn from follow-up or lost to follow-up prior to the scheduled end of treatment of study treatment, except for pregnancies and violent or accidental death that are instead classified as having a Not Assessable outcome (see SAP section 4.1.3).
4. Participants who had an Mtb Positive culture result when last seen during or prior to the Month 12 analysis visit window, whether confirmed by a second sample or not, unless determined to have been re-infected.
5. Participants receiving any one or more of the following, except when given for failure or recurrence subsequently shown to be a reinfection with a strain of M. tuberculosis, different from that or those identified at study entry through genotyping methods):
    a) Extension of treatment beyond that permitted by the protocol; excepting
        a. Temporary drug re-challenge;
        b. Over-treatment with drugs from assigned study kits;

c. Twenty-one days or fewer of non-study anti-TB medications given for treatment of active TB; or
d. Secondary isoniazid preventative therapy in HIV infected participants.

b) Re-start of treatment for active TB;

c) Change in treatment (including frequency or dosage) for any reason except re-infection, pregnancy, or temporary drug challenge.

6. Participants who die during the follow-up phase (as defined in SAP section 4.6) where the cause of death is considered related to tuberculosis.

2.4.3 Cure (Favorable)

A participant will be classified as having a favorable outcome if any one of the following conditions is met and an unfavorable outcome has not occurred:

1. Participants whose last culture result during the Month 12 analysis visit window is Mtb Negative (See SAP section 4.7).
2. Participants who are seen during the Month 12 analysis visit window and are clinically without symptoms/signs of ongoing active TB (indicated by absence of initiation of possible poor treatment response evaluation or PPTR that does not indicate presence of symptoms/signs of ongoing active TB), and have achieved culture conversion prior to Month 12, and
    1. Are unable to produce a sputum specimen at any point during the Month 12 analysis visit window; or
    2. Produce a sputum specimen that is contaminated or unevaluable without evidence of *M. tuberculosis,* and no sputum specimens yield positive or negative culture results during the Month 12 analysis visit window.

2.4.4 Not Assessable

A participant will be classified as having a Not Assessable outcome if any one of the following conditions is met and an unfavorable outcome has not occurred:

1. Participants not otherwise classified as unfavorable, but do not attend a visit within the Month 12 analysis visit window, and their last culture result is negative for *M. tuberculosis.*
2. Women who become pregnant during assigned study treatment (see SAP section 4.6 for definition of study treatment phase).
3. Participants who die during the follow-up phase (as defined in SAP section 4.6) of any cause that is not considered related to tuberculosis.
4. Participants who die from a violent (e.g. homicide) or accidental (e.g. road traffic) cause during their assigned study treatment (see SAP section 4.6 for definition of study treatment phase). As above, suicide will be considered an unfavorable outcome.
5. Participants who are:
    a) Retreated, or have treatment changed or extended; and
    b) Demonstrated to be re-infected with a strain of M. tuberculosis, different from that or those identified at study entry through genotyping methods.

A participant classified as having a Not Assessable outcome will be excluded from the Assessable and Adherent Per-Protocol analyses, but considered as Unfavorable for other analyses.

2.5 Analysis populations

2.5.1 Participants Randomized in Error

Participants who were randomized in error are those who were found to not meet eligibility criteria after enrollment, other than criteria in SAP section 4.3, relating to microbiology.

Determination of whether eligibility criteria was violated and subsequent classification as 'randomized in error' will be based only on data that was collected prior to randomization. All participants who are found to be in violation of any eligibility criteria (other than the criteria in SAP section 4.3 relating to microbiology) will be classified as randomized in error, irrespective of whether the participant was withdrawn from treatment or not.

2.5.2 Criteria for exclusion after enrollment ('Late exclusion')

Microbiological confirmation of drug-susceptible tuberculosis is not expected always to be available at the time of enrollment. Enrolled individuals who are subsequently determined to meet either of the following criteria will be classified as 'late exclusions' and study treatment will be discontinued:

A. Screening, baseline, and Week 2 study visit sputum cultures all fail to grow *M. tuberculosis*.
B. *M. tuberculosis* cultured or detected through molecular assays (Cepheid Xpert MTB/RIF or Hain MTBDRplus assays) from sputum obtained around the time of study entry is determined subsequently to be resistant to one or more of isoniazid, rifampin, or fluoroquinolones.

2.5.3 Adequate treatment

Only participants having completed an adequate number of study doses will be included in the Per Protocol (PP) analysis populations. Two PP analysis populations are defined. PP75 excludes participants who have received less than approximately 75% of study doses (see Table below for exact doses required) using the definitions consistent with previous phase III TB trials, in particular the REMoxTB trial[3] and in the original trials which determined the effectiveness of the control 6 month isoniazid-rifampin regimen[4]. The TB-REFLECT analyses[5] have shown that even participants with less than 95% adherence have poorer outcomes than those with perfect adherence, and consecutive missed doses is associated with poorer outcomes than occasional missed doses[6]. For these reasons, the PP95 analysis population excludes participants who have received less than approximately 95% of study doses (see Table A below for exact doses required). PP95 will be the primary per protocol analysis population with PP75 being supportive.

Table A. Two definitions of adequate treatment

	75% Adherence (PP75) Approximately 75% of doses within 125% of the intended duration.		95% Adherence (PP95) Approximately 95% of doses within 125% of the intended duration.	
	Doses	Days	Doses	Days since treatment initiation
Regimen 1	At least 42 intensive phase doses	No more than 70 days since treatment initiation	At least 54 intensive phase doses	No more than 70 days since treatment initiation
	At least 84 continuation phase doses	No more than 168 days since completing intensive phase	At least 120 continuation phase doses	No more than 168 days since completing intensive phase
	No more than 42 doses missed		No more than 5 consecutive DOT doses missed	
Regimens 2 or 3	At least 42 intensive phase doses	No more than 70 days since treatment initiation	At least 54 intensive phase doses	No more than 70 days since treatment initiation
	At least 42 continuation phase doses	No more than 84 days since completing intensive phase	At least 60 continuation phase doses	No more than 84 days since completing intensive phase
	No more than 28 doses missed		No more than 5 consecutive DOT doses missed	

2.5.4 Intention-to-Treat (ITT)

Includes all enrolled participants who receive a treatment assignment.

2.5.5 Microbiologically Eligible

Includes the subset of Intention-to-Treat participants who, in addition, have culture confirmation of drug-susceptible tuberculosis at study entry. Participants classified as 'not assessable' will be considered to have an unfavorable outcome.

2.5.6 Assessable

Includes the subset of Microbiologically Eligible participants who, in addition, are not classified as 'not assessable'.

2.5.7 Adherent Per-Protocol (PP95)

Includes the subset of Assessable participants who, receive 95% of assigned treatment as defined in SAP section 4.4. Participants in the Assessable study population that do not complete adequate treatment for the reason of death or bacteriological treatment failure will be included in the PP95 analysis population provided they receive 95% of doses up to the time of treatment withdrawal. This will be the primary PP analysis population.

2.5.8 Adherent Per-Protocol (PP75)

Includes the subset of Assessable participants who, receive 75% of assigned treatment as defined in SAP section 4.4. Participants in the Assessable study population that do not complete adequate treatment for the reason of death or bacteriological treatment failure will be included in the PP75 analysis population provided they receive 75% of doses up to the time of treatment withdrawal. This is a supportive PP analysis population and is included for comparability with previous trials (particularly REMoxTB)

2.6 Sensitivity Analyses

The following additional sensitivity analyses were conducted:

1. The primary efficacy analysis will be repeated in the Microbiologically Eligible study population where all participants classified as not assessable will be classified as favorable rather than unfavorable.
2. The primary efficacy analysis will be repeated in the Microbiologically Eligible and Assessable study populations where participants taking any non-study anti-TB medications for more than 21 days for any reason (including secondary isoniazid preventative therapy) will instead be classified as unfavorable.
3. The primary efficacy analysis will be repeated in the Microbiologically Eligible and Assessable study populations where participants taking any non-study anti-TB medications for more than 5 days for any reason (including secondary isoniazid preventative therapy) will instead be classified as unfavorable.
4. The primary efficacy analysis will be repeated with a modification to the definitions of 'Absence of Cure' using the following text to replace the paragraph numbered 1 in SAP section 4.1.1. of the Statistical Analysis Plan v2.0 (SAP v2.0) so that intervening negative cultures are ignored in the determination of absence of bacteriological cure:
   *A participant will be considered to have absence of bacteriological cure if he/she has a sputum sample, obtained at or after Week 17 and no later than the end of the Month 12 analysis visit window, that is Mtb Culture Positive (*see SAP *section 4.7 of the SAP v2.0 for definitions of culture results) that is indistinguishable from the initial isolate (see separate sequencing plan for definitions), and this is confirmed by a second sample that is Mtb culture positive. A second confirmatory sample, on a different day (**irrespective of intervening Mtb Negative culture results)**, is required, as a single positive sputum culture result in isolation will not be considered absence of bacteriological cure. If results from*

strain analysis are inconclusive or unavailable, it will be assumed that strains were indistinguishable.

5. The primary efficacy analysis will be repeated reclassifying all exogenous reinfections as unfavorable.
6. The primary efficacy analysis will be repeated considering only culture inoculation results from MGIT liquid media and ignoring any culture inoculation results from solid media.
7. The primary efficacy analysis will be repeated considering only culture inoculation results from solid media and ignoring any culture inoculation results from MGIT liquid media.
8. The primary efficacy analysis will be repeated in the Microbiologically Eligible and Assessable study populations excluding additionally participants for whom none of screening or baseline study visit sputum cultures are Mtb Positive (week 2 sputum cultures will not be used for determining late exclusions).
9. The primary efficacy analysis will be repeated in the Microbiologically Eligible and Assessable study populations including all participants classified as randomized in error. For such patients, the classification of the outcome will follow the algorithm in SAP section 4.1.
10. The primary efficacy analysis will be repeated relaxing the criteria for evaluable cultures by removing the inoculation result classification of 'Unevaluable' so that inoculations are reclassified as positive, negative, contaminated, or missing.
11. The primary efficacy analysis will be repeated reclassifying participants classified as Not Assessable because they did not attend a visit within the Month 12 analysis visit window based on the immediate next data available for the participant after the Month 12 analysis visit window. If the patient is culture negative at the next visit after the Month 12 visit window, they will be classified in this analysis as favorable, if they are culture positive at the next visit at the Month 12 visit window, they will be classified in this analysis as unfavorable. This sensitivity analysis will be interpreted with caution as, at the time of the 12-month primary analysis when all participants will not have completed 18 months of follow-up, it will include a mix of month 15 and month 18 data.
12. The primary efficacy analysis will be repeated reclassifying patients that have two positive cultures but do not have subsequent restart of treatment as favorable rather than unfavorable.
13. The primary efficacy analysis will be repeated with modified analysis visit windows for visits after Month 9 according to the following table:

Visit	**Target date (days from date of first dose of treatment)**	**SAP v2.0 Analysis window for primary analysis**	**Analysis window for sensitivity analysis**
Month 9	270	263-352	263-**345**
Month 12	360	353-442	**346**-442
Month 15	450	443-523	443-**509**

Month 18	540	533-no upper bound (an upper bound of 570 will be used for reporting safety analyses)	**510**-no upper bound (an upper bound of 570 will be used for reporting safety analyses)

The analysis visit windows for the primary Month 12 visit and the end of follow-up Month 18 visit extend to 14 and 30 days prior to the target date of visit respectively (rather than 7 days for other study visits) since these are critical visits for the primary and end of follow-up efficacy analyses.

14. The primary efficacy analysis will be repeated reclassifying as Cure (Favorable) those participants who have not achieved culture conversion prior to Month 12, but are otherwise seen during the Month 12 analysis visit window and are clinically without symptoms/signs or ongoing active TB and fulfill all the other criteria under the second item under SAP section 4.1.2. of the SAP v2.0.

2.7 Sub-group Analyses

The primary efficacy analysis will be repeated in subgroups according to the following baseline factors (i.e. those present at enrollment or from study-specific samples collected for screening and baseline visits). For factors reliant on results from sputum samples, the results must be from the study laboratory of record. Categorical variables will be split by tertiles except where there is previous clinical justification for a different cut-off.

The following sub-groups were pre-specified in the Statistical Analysis Plan prior to database lock.

- HIV status
- Presence of cavitation on baseline chest radiograph*
- Extent of cavitation on baseline chest radiograph
- Sex
- Weight
- BMI
- WHO scale smear quantification
- Solid culture colony count
- MGIT days to detection
- GeneXpert MTB/RIF Cycle Threshold
- Age
- Country of study center
- Smoking history
- History of diabetes
- Ethnicity and race

The test for an interaction between the covariate and treatment will be done using logistic regression comparing the model including the interaction term and the model with only

marginal terms using the likelihood ratio test to evaluate the statistical significance of inclusion of the interaction term in the model.

*cavitation was defined as a gas-containing lucent space at least 1 cm in diameter within the lung parenchyma surrounded by an infiltrate or fibrotic wall greater than 1 mm thick see on the chest radiograph. Cavitation seen only on chest tomography (e.g. CT), if performed, did not satisfy this definition.

3 Supplementary Tables and Figures cited in the text

Figure S1. Study S31/A5349 schema

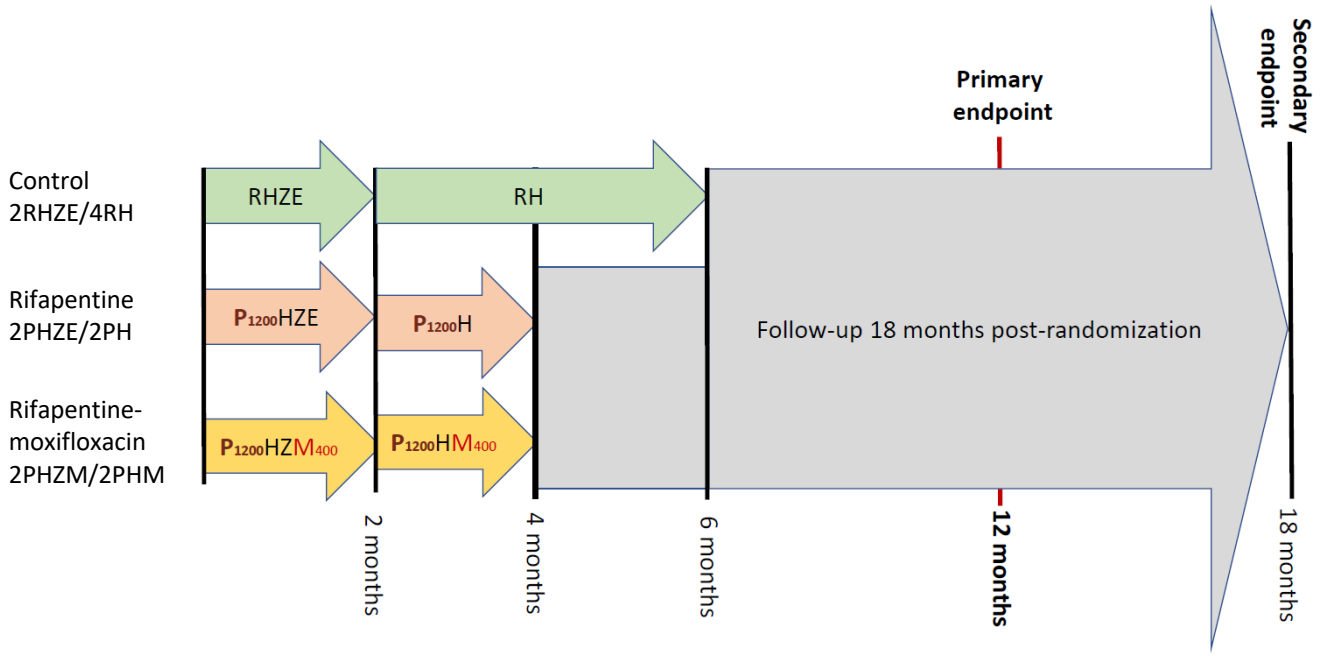


Table S1. Doses of study medications by body weight

Drug	Dose
Rifapentine	1200 mg
Moxifloxacin	400 mg
Rifampin	600 mg
Isoniazid	300 mg
Pyrazinamide	
< 55 kg	1000 mg
≥ 55-75 kg	1500 mg
> 75 kg	2000 mg
Ethambutol	
< 55 kg	800 mg
≥ 55-75 kg	1200 mg
> 75 kg	1600 mg
Vitamin B6	25 or 50 mg (based on local site norms)

Notes

Drugs and doses used to initiate treatment were assigned by the enrollment application, based on weight reported at enrollment, and doses for pyrazinamide and ethambutol were adjusted for the participant's weight that is recorded at the most recent scheduled study visit.

All drugs were administered orally, seven days per week, throughout treatment. Individual drugs were used; fixed dose combination preparations were not used. Five of seven doses per week were given as directly observed therapy (DOT) by study personnel, or by a healthcare worker or lay treatment supervisor who was aware of the study protocol and trained regarding the study protocol. Doses on weekends and on holidays up to three consecutive days were either DOT or self-administered. Per written study procedures, participants receiving a rifapentine-containing investigational regimen should take study drugs within one hour after ingesting food. Participants receiving a rifampin-containing investigational regimen should take study drugs on an empty stomach; for participants on rifampin who have difficulty tolerating study drugs on an empty stomach administration with food was acceptable.

Table S2. Schedule of participant evaluations

Schedule of procedures/evaluations.

Visit window	Screen	Up to 7 days after screen	+/− three (3) days						+/− seven (7) days					Possible poor treatment response	Post early termination visit[f]
Visit		Baseline	WK 2	WK 4	WK 8	WK 12	WK 17	WK 22	WK 26	MO 9	MO 12	MO 15	MO 18		
Informed consent	X														
Inclusion/Exclusion	X	X													
Demographics, medical history	X														
Contact information	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptoms		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X						X
Interval medical history										X	X	X	X	X	
Height	X														
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest radiograph	X						X[e]		X[e]					X	
Visual tests		X		X											
HIV test	X														
CD4, HIV viral load (if HIV-pos)	X[a]														
Pregnancy testing	X														
Randomization		X													
Sputum for smear and culture[b]	X	X	X	X	X	X	XX	XX	XX	XX	XX[c]	XX	XX[c]	XXX	
Sputum for rapid molecular test, if available at site	X														
Storage of Mtb bacterial isolate	X	X					X	X	X	X	X	X	X	X	
Diabetes screen[d]	X														
ALT, bilirubin, creatinine, hemoglobin, WBC with differential, platelets	X		X	X	X	X	X	X							X
Serum albumin, potassium	X														
PK sampling for TB drugs			within this interval												
Blood sample for pharmacogenomics			Obtain any time after enrollment												
EFV1: Plasma for EFV PK	At screening or baseline			X	X		X								
EFV1: HIV viral load	At screening or baseline				X		X								
EFV2: Plasma for EFV PK				Obtain at about 4 weeks after starting EFV AND at about 8 weeks after starting EFV				X							
EFV2: HIV viral load	Required per eligibility criteria			Obtain once at about 8 weeks after starting EFV				X							
Sputum, blood, urine for research		X	X	X	X		X[e]		X[e]					X	
Contact central study clinician														X	

[a] Unless results of a test performed at or within 30 days prior to screening are available.

[b] All sputa should be sent to the designated study laboratory with the exception of the screening specimen, which may be evaluated at any locally acceptable laboratory. If a screening specimen has been found to be smear or culture positive at a non-study laboratory, then either store the isolate if culture positive from the non-study laboratory or get an additional specimen for culture and storage of isolate. Two specimens (i.e. one at screening and one at baseline) are required prior to initiation of study treatment. At least two (2) sputa should be obtained at each of weeks 17, 22, 26 and at each of months 9, 12, 15, and 18.

[c] If both of the month 12 sputa or both of the month 18 sputa are contaminated, then the participant should be asked to provide at least two (2) additional sputa as soon as possible after contamination is recognized.

[d] Hemoglobin A1C is the preferred test. If such testing is not available, then fasting or random blood glucose can be measured.

[e] To be obtained at the end-of-study treatment visit (i.e. either week 17 or week 26).

[f] This visit occurs approximately 14 days after stopping study drugs.

Table S3. Primary efficacy outcome analysis results for the PP75 and PP95 analysis populations

	Per-protocol 75% (PP75)				Per-protocol 95% (PP95)			
	Control	Rifapentine-moxifloxacin	Rifapentine regimen	All	Control	Rifapentine-moxifloxacin	Rifapentine regimen	All
Total in analysis population	673	706	715	2094	563	641	650	1854
Cure – no. (%)								
Participants with outcome	652 (96.9%)	663 (93.9%)	640 (89.5%)	1955 (93.4%)	548 (97.3%)	604 (94.2%)	579 (89.1%)	1731 (93.4%)
Culture negative status at month 12	639 (94.9%)	651 (92.2%)	631 (88.3%)	1921 (91.7%)	537 (95.4%)	592 (92.4%)	570 (87.7%)	1699 (91.6%)
Seen at month 12 but no sputum produced, or cultures contaminated or unevaluable	13 (1.9%)	12 (1.7%)	9 (1.3%)	34 (1.6%)	11 (2.0%)	12 (1.9%)	9 (1.4%)	32 (1.7%)
Absence of cure – no. (%)								
Participants with outcome	21 (3.1%)	43 (6.1%)	75 (10.5%)	139 (6.6%)	15 (2.7%)	37 (5.8%)	71 (10.9%)	123 (6.6%)
Tuberculosis-related absence of cure	19 (2.8%)	41 (5.8%)	73 (10.2%)	133 (6.4%)	15 (2.7%)	36 (5.6%)	70 (10.8%)	121 (6.5%)
Two consecutive positive cultures at or after week 17	11 (1.6%)	30 (4.2%)	63 (8.8%)	104 (5.0%)	9 (1.6%)	27 (4.2%)	61 (9.4%)	97 (5.2%)
Not seen at month 12; last culture positive	6 (0.9%)	3 (0.4%)	2 (0.3%)	11 (0.5%)	5 (0.9%)	3 (0.5%)	2 (0.3%)	10 (0.5%)
Clinical diagnosis of tuberculosis recurrence and treatment restarted	2 (0.3%)	8 (1.1%)	8 (1.2%)	18 (0.8%)	1 (0.2%)	6 (0.9%)	7 (1.1%)	14 (0.8%)
Not tuberculosis-related absence of cure	2 (0.3%)	2 (0.3%)	2 (0.3%)	121 (5.2%)	0	1 (0.2%)	1 (0.2%)	2 (0.1%)
Death during treatment	1 (0.1%)	1 (0.1%)	2 (0.3%)	4 (0.2%)	0	1 (0.2%)	1 (0.2%)	2 (0.1%)
Lost to follow-up during treatment	1 (0.1%)	0	0	1 (0.0%)	0	0	0	0
Treatment changed or restarted for other reasons	0	1 (0.1%)	0	1 (0.0%)	0	0	0	0
Adjusted difference from control in percentage with cure (95% CI)	**N/A**	**3.0 (0.8, 5.2)**	**7.3 (4.7, 9.9)**	**N/A**	**N/A**	**3.1 (0.9, 5.3)**	**8.2 (5.5, 11.0)**	**N/A**
Unadjusted difference from control in percentage with cure (95% CI)	**N/A**	**3.0 (0.8, 5.2)**	**7.4 (4.8, 10.0)**	**N/A**	**N/A**	**3.1 (0.9, 5.4)**	**8.3 (5.5, 11.0)**	**N/A**

N/A, not applicable

Table S4. Secondary ITT and Sensitivity analysis results: #1 - #14

Sensitivity Analysis		Control (2RHZE/4RH)	Rifapentine-moxifloxacin (2PHZM/2PHM)	Rifapentine (2PHZE/2PH)	Total
ITT	Total in analysis	**829**	**849**	**838**	**2516**
(Secondary)	Favorable	656 (79.1%)	668 (78.7%)	645 (77.0%)	1969 (78.3%)
	Unfavorable	173 (20.9%)	181 (21.3%)	193 (23.0%)	547 (21.7%)
	Adjusted difference (95% CI)		0.4 (-3.5, 4.3)	2.1 (-1.8, 6.1)	
	Unadjusted difference (95% CI)		0. 5 (-3.5, 4.4)	2.2 (-1.8, 6.1)	
#1	Total in analysis	726	756	752	2234
	Favorable	656 (90.4%)	668 (88.4%)	645 (85.8%)	1969 (88.1%)
	Unfavorable	70 (9.6%)	88 (11.6%)	107 (14.2%)	265 (11.9%)
	Adjusted difference (95% CI)		2.0 (-1.1, 5.1)	4.4 (1.2, 7.7)	
	Unadjusted difference (95% CI)		2.0 (-1.1, 5.1)	4.6 (1.3, 7.9)	
#2	Total in analysis	726	756	752	2234
	Favorable	656 (90.4%)	668 (88.4%)	645 (85.8%)	1969 (88.1%)
	Unfavorable	70 (9.6%)	88 (11.6%)	107 (14.2%)	265 (11.9%)
	Adjusted difference (95% CI)		2.0 (-1.1, 5.1)	4.4 (1.2, 7.7)	
	Unadjusted difference (95% CI)		2.0 (-1.1, 5.1)	4.6 (1.3, 7.9)	
#3	Total in analysis	726	756	752	2234
	Favorable	656 (90.4%)	668 (88.4%)	645 (85.8%)	1969 (88.1%)
	Unfavorable	70 (9.6%)	88 (11.6%)	107 (14.2%)	265 (11.9%)
	Adjusted difference (95% CI)		2.0 (-1.1, 5.1)	4.4 (1.2, 7.7)	
	Unadjusted difference (95% CI)		2.0 (-1.1, 5.1)	4.6 (1.3, 7.9)	
#4	Total in analysis	726	756	752	2234
	Favorable	656 (90.4%)	668 (88.4%)	645 (85.8%)	1969 (88.1%)
	Unfavorable	70 (9.6%)	88 (11.6%)	107 (14.2%)	265 (11.9%)
	Adjusted difference (95% CI)		2.0 (-1.1, 5.1)	4.4 (1.2, 7.7)	
	Unadjusted difference (95% CI)		2.0 (-1.1, 5.1)	4.6 (1.3, 7.9)	
#5	Total in analysis	728	756	753	2237
	Favorable	656 (90.1%)	668 (88.4%)	645 (85.7%)	1969 (88.0%)
	Unfavorable	72 (9.9%)	88 (11.6%)	108 (14.3%)	268 (12.0%)
	Adjusted difference (95% CI)		2.0 (-1.1, 5.1)	4.3 (1.0, 7.6)	
	Unadjusted difference (95% CI)		2.0 (-1.1, 5.1)	4.5 (1.1, 7.8)	
#6	Total in analysis	725	756	750	2229
	Favorable	656 (90.5%)	668 (88.6%)	644 (85.9%)	1968 (88.3%)
	Unfavorable	69 (9.5%)	86 (11.4%)	106 (14.1%)	261 (11.7%)
	Adjusted difference (95% CI)		1.9 (-1.2, 5.0)	4.5 (1.2, 7.7)	
	Unadjusted difference (95% CI)		1.9 (-1.2, 5.0)	4.6 (1.3, 7.9)	
#7	Total in analysis	725	754	750	2229
	Favorable	656 (90.5%)	668 (88.6%)	644 (85.9%)	1968 (88.3%)
	Unfavorable	69 (9.5%)	86 (11.4%)	106 (14.1%)	261 (11.7%)

Sensitivity Analysis		Control (2RHZE/4RH)	Rifapentine-moxifloxacin (2PHZM/2PHM)	Rifapentine (2PHZE/2PH)	Total
	Adjusted difference (95% CI)		1.9 (-1.2, 5.0)	4.5 (1.2, 7.7)	
	Unadjusted difference (95% CI)		1.9 (-1.2, 5.0)	4.6 (1.3, 7.9)	
#8	Total in analysis	717	748	744	2209
	Favorable	647 (90.2%)	660 (88.2%)	638 (85.8%)	1945 (88.1%)
	Unfavorable	70 (9.8%)	88 (11.8%)	106 (14.3%)	264 (12.0%)
	Adjusted difference (95% CI)		2.0 (-1.2, 5.2)	4.3 (1.1, 7.6)	
	Unadjusted difference (95% CI)		2.0 (-1.2, 5.2)	4.5 (1.2, 7.8)	
#9	Total in analysis	732	759	757	2248
	Favorable	659 (90.0%)	668 (88.0%)	647 (85.5%)	1974 (87.8%)
	Unfavorable	73 (10.0%)	91 (12.0%)	110 (14.5%)	274 (12.2%)
	Adjusted difference (95% CI)		2.0 (-1.1, 5.2)	4.4 (1.1, 7.7)	
	Unadjusted difference (95% CI)		2.0 (-1.2, 5.2)	4.6 (1.2, 7.9)	
#10	Total in analysis	726	756	752	2234
	Favorable	657 (90.5%)	668 (88.4%)	645 (85.8%)	1970 (88.2%)
	Unfavorable	69 (9.5%)	88 (11.6%)	107 (14.2%)	264 (11.8%)
	Adjusted difference (95% CI)		2.2 (-1.0, 5.3)	4.6 (1.3, 7.8)	
	Unadjusted difference (95% CI)		2.1 (-1.0, 5.3)	4.7 (1.4, 8.0)	
#11	Total in analysis	741	766	764	2271
	Favorable	671 (90.6%)	678 (88.5%)	657 (86.0%)	2006 (88.3%)
	Unfavorable	70 (9.5%)	88 (11.5%)	107 (14.0%)	265 (11.7%)
	Adjusted difference (95% CI)		2.0 (-1.0, 5.1)	4.4 (1.2, 7.6)	
	Unadjusted difference (95% CI)		2.0 (-1.1, 5.1)	4.6 (1.3, 7.8)	
#12	Total in analysis	726	756	752	2234
	Favorable	659 (90.8%)	669 (88.5%)	645 (85.8%)	1973 (88.3%)
	Unfavorable	67 (9.2%)	88 (11.5%)	107 (14.2%)	261 (11.7%)
	Adjusted difference (95% CI)		2.3 (-0.8, 5.4)	4.9 (1.6, 8.1)	
	Unadjusted difference (95% CI)		2.3 (-0.8, 5.4)	5.0 (1.7, 8.3)	
#13	Total in analysis	727	756	753	2236
	Favorable	657 (90.4%)	668 (88.4%)	646 (85.8%)	1971 (88.2%)
	Unfavorable	70 (9.6%)	88 (11.6%)	107 (14.2%)	265 (11.9%)
	Adjusted difference (95% CI)		2.0 (-1.1, 5.2)	4.4 (1.2, 7.7)	
	Unadjusted difference (95% CI)		2.0 (-1.1, 5.2)	5.6 (1.3, 7.9)	
#14	Total in analysis	727	756	752	2235
	Favorable	657 (90.4%)	668 (88.4%)	645 (85.8%)	1970 (88.1%)
	Unfavorable	70 (9.6%)	88 (11.6%)	107 (14.2%)	265 (11.9%)
	Adjusted difference (95% CI)		2.0 (-1.1, 5.2)	4.5 (1.2, 7.7)	
	Unadjusted difference (95% CI)		2.0 (-1.1, 5.2)	5.6 (1.3, 7.9)	

Figure S2. Sensitivity analyses: Rifapentine-Moxifloxacin regimen (2PHZM/2PHM) vs. Control regimen (2RHZE/4RH)

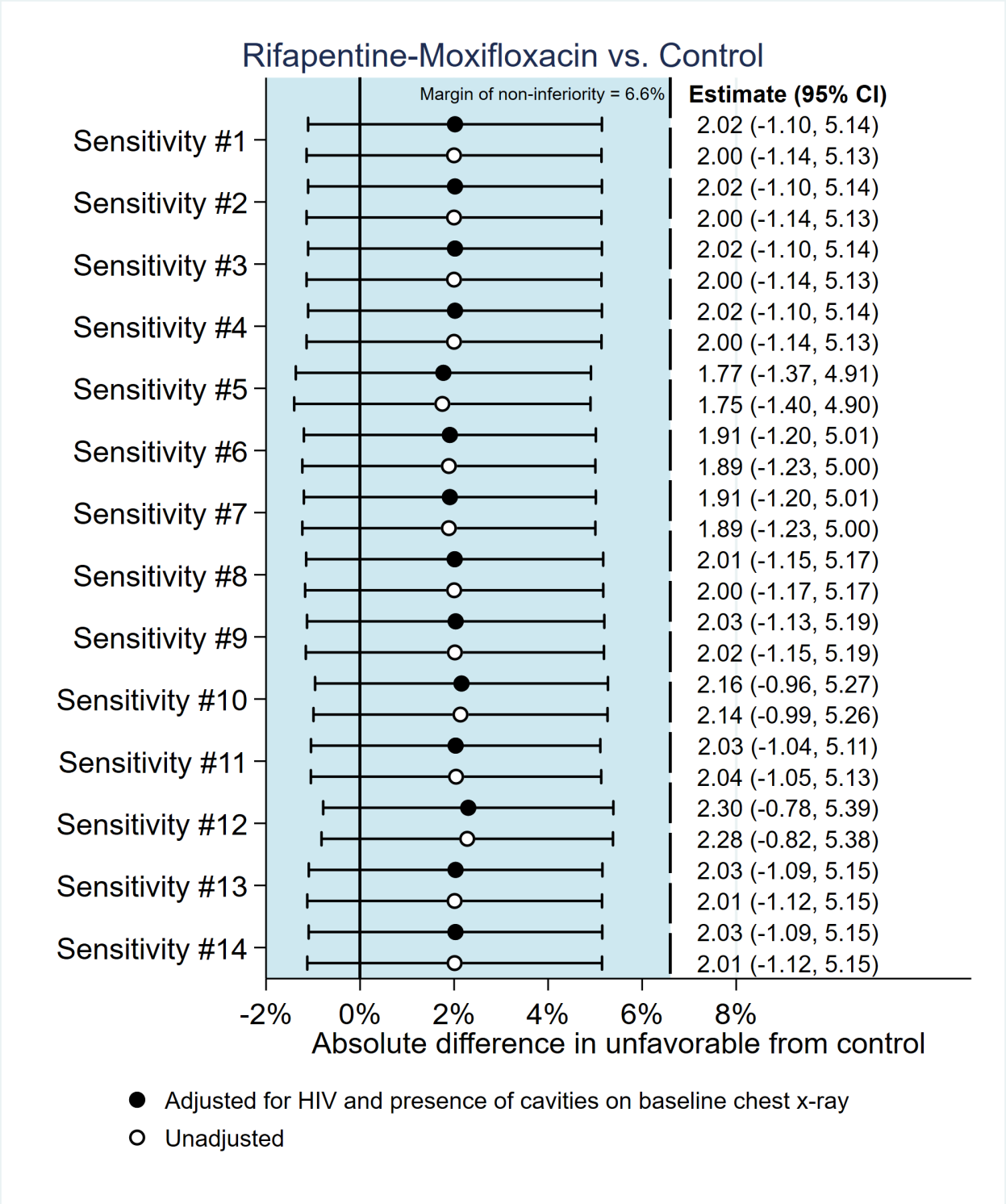


Figure S3. Sensitivity analyses: Rifapentine- regimen vs. Control regimen

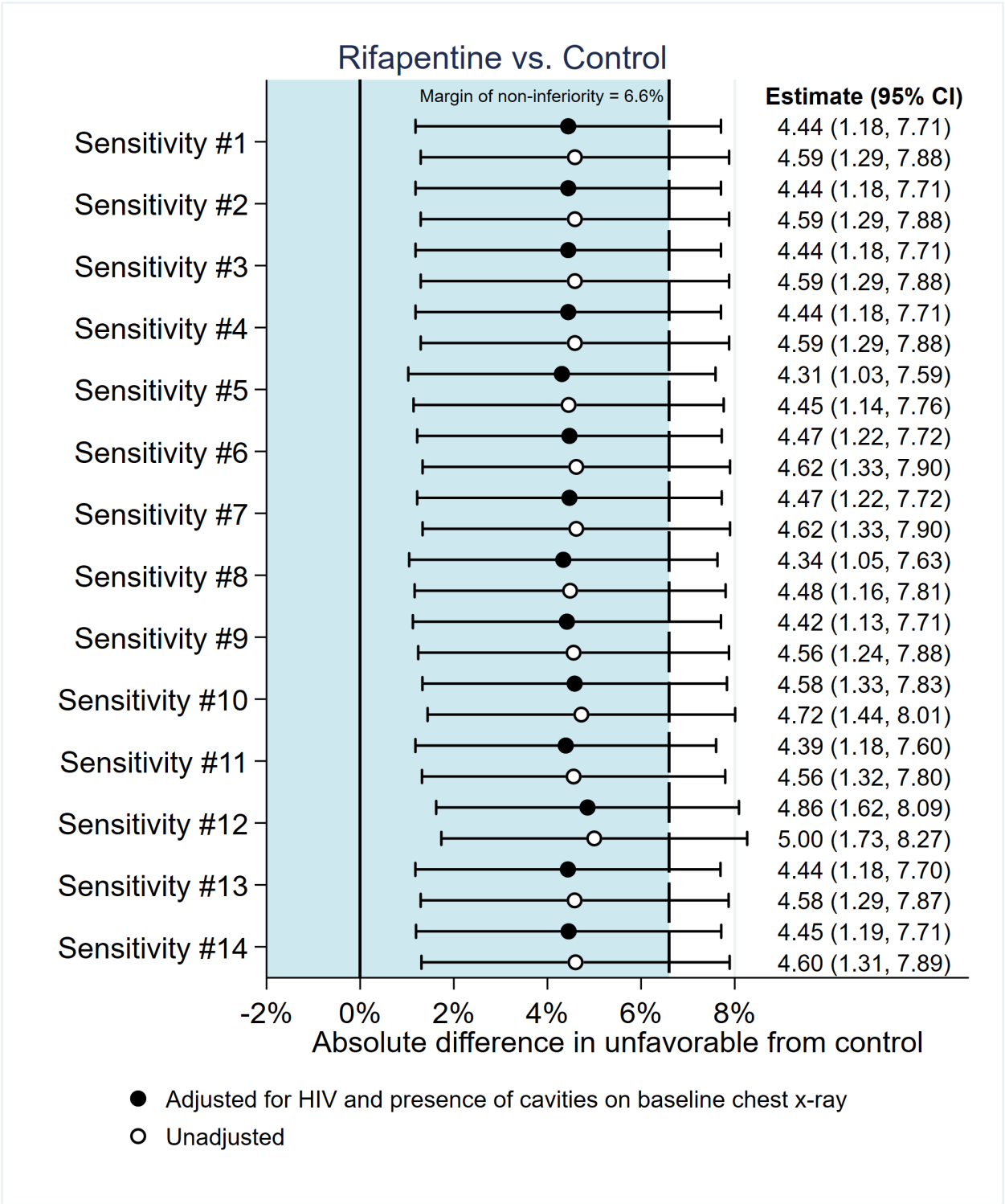
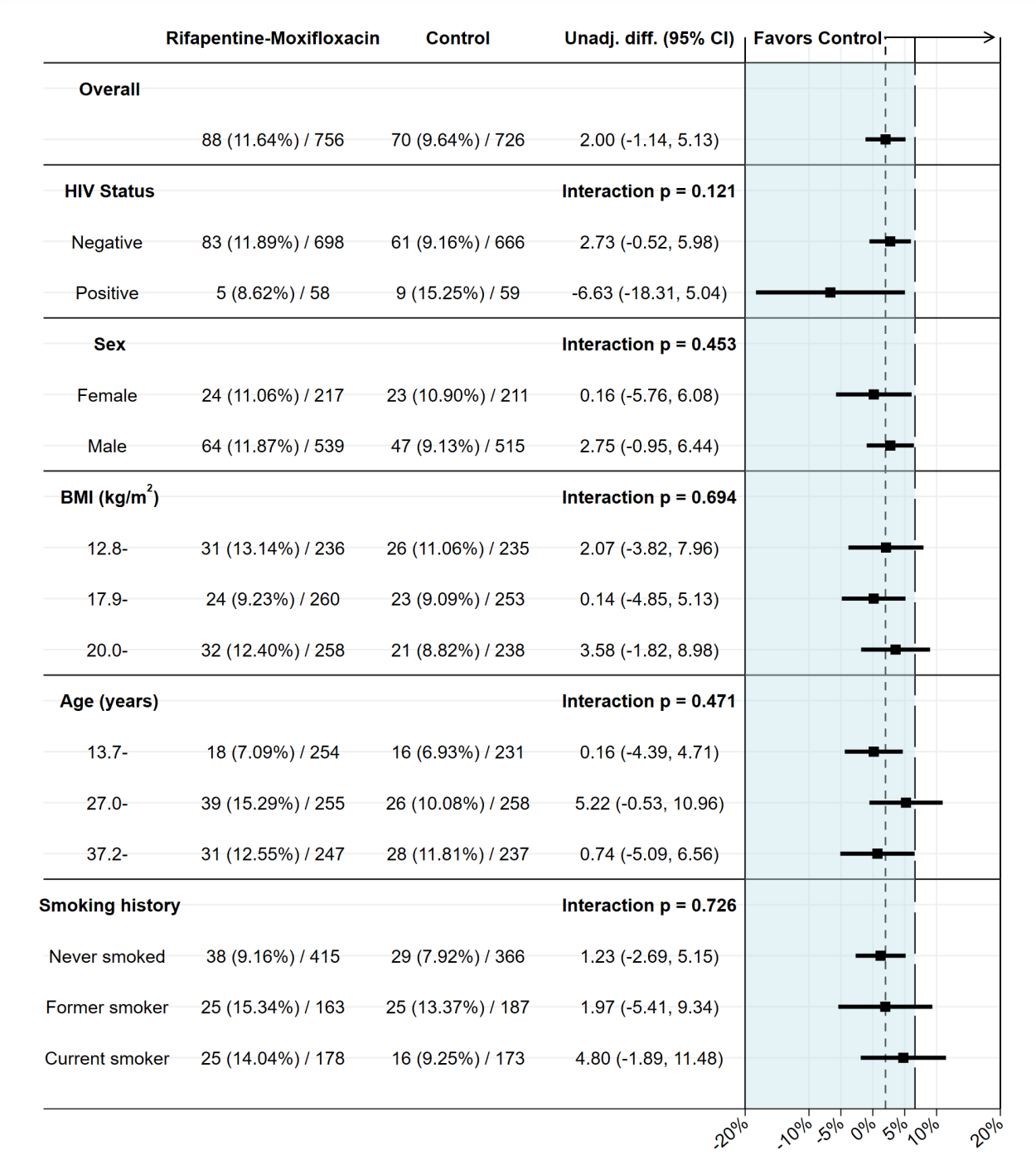
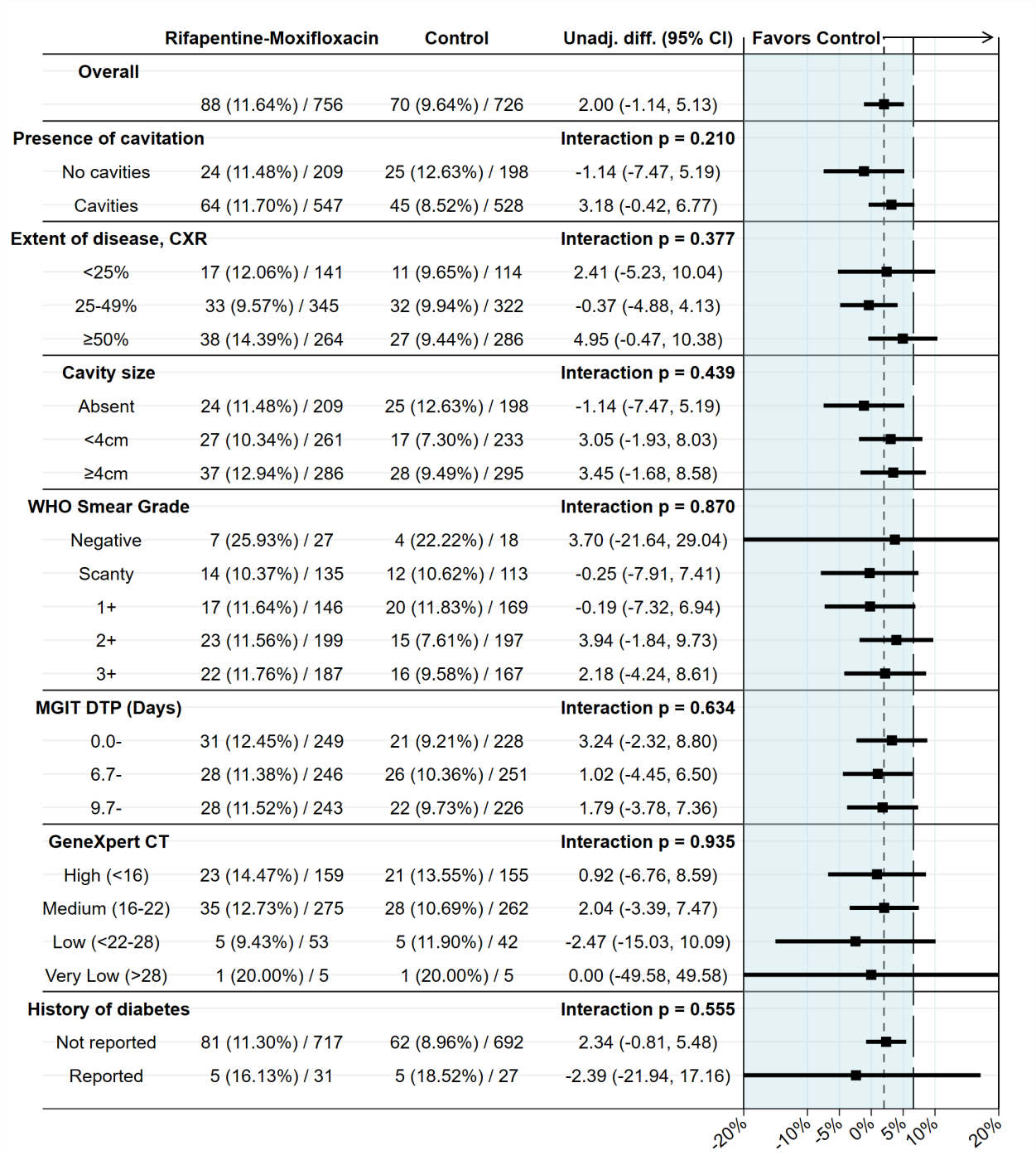


Figure S4a. Subgroup analyses: assessable analysis population, rifapentine-moxifloxacin regimen (2PHZM/2PHM) vs. control regimen (2RHZE/4RH) (Part a)



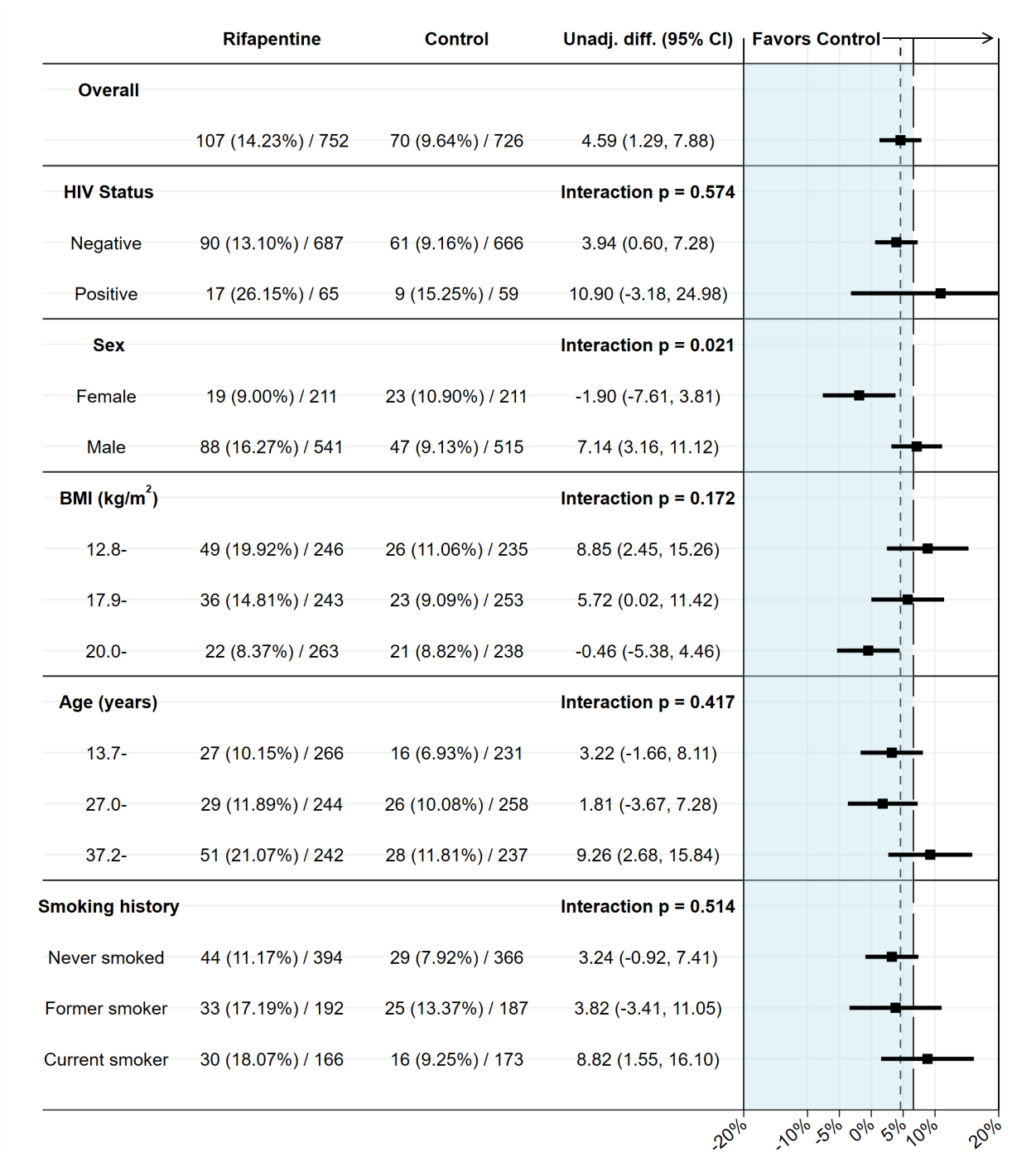
First two columns show unfavourable outcomes N(%) / participants in Primary: Assessable analysis population.
Dashed lines indicate overall unadjusted difference (short dashes) and margin of non-inferiority (6.6%, long dashes).

Figure S4b. Subgroup analyses: assessable analysis population, rifapentine-moxifloxacin regimen (2PHZM/2PHM) vs. control regimen (2RHZE/4RH) (Part b)



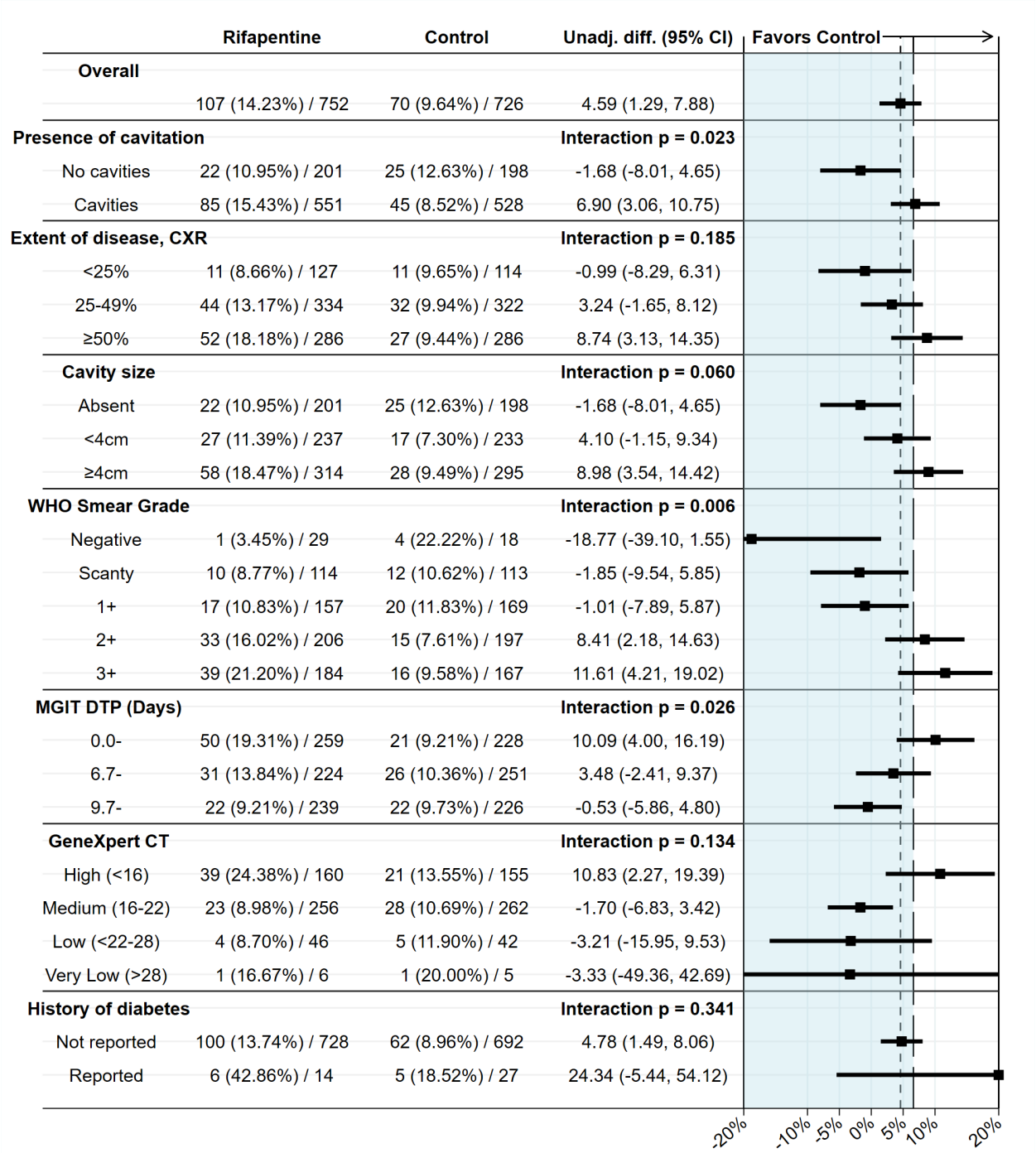
First two columns show unfavourable outcomes N(%) / participants in Primary: Assessable analysis population.
Dashed lines indicate overall unadjusted difference (short dashes) and margin of non-inferiority (6.6%, long dashes).

Figure S5a. Subgroup analyses: assessable analysis population, rifapentine regimen (2PHZE/2PH) vs. control regimen (2RHZE/4RH) (Part a)



First two columns show unfavourable outcomes N(%) / participants in Primary: Assessable analysis population.
Dashed lines indicate overall unadjusted difference (short dashes) and margin of non-inferiority (6.6%, long dashes).

Figure S5b. Subgroup analyses: assessable analysis population, rifapentine regimen (2PHZE/2PH) vs. control regimen (2RHZE/4RH) (Part b)



First two columns show unfavourable outcomes N(%) / participants in Primary: Assessable analysis population.
Dashed lines indicate overall unadjusted difference (short dashes) and margin of non-inferiority (6.6%, long dashes).

Table S5. Analysis of time to culture conversion in liquid media: microbiologically eligible analysis population

Statistic	Control (2RHZE/4RH)	Rifapentine-moxifloxacin (2PHZM/2PHM)	Rifapentine (2PHZE/2PH)
25th centile, weeks	8.00	4.14	4.14
Median (50th centile), weeks	8.14	8.14	8.14
75th centile, weeks	12.14	8.29	12.00
Proportion with culture conversion at 8 weeks*	63.40%	78.50%	74.20%
Proportion with culture conversion at 12 weeks*	86.60%	90.50%	89.50%
Hazard ratio (95% CI)**	Reference	1.38 (1.24, 1.54)	1.28 (1.15, 1.42)

*Since scheduled study visits did not necessarily occur exactly at 8 weeks, the proportion with culture conversion at 8 weeks is estimated from the Kaplan-Meier estimator at t = 10 weeks, and the proportion with culture conversion at 12 weeks as t = 14 weeks.

**There was evidence that the proportional hazard assumption was violated for time to culture conversion on liquid and solid media and therefore the hazard ratio should be interpreted with caution as a representative metric of differences between arms.

Figure S6. Analysis of time to culture conversion in liquid media: microbiologically eligible analysis population

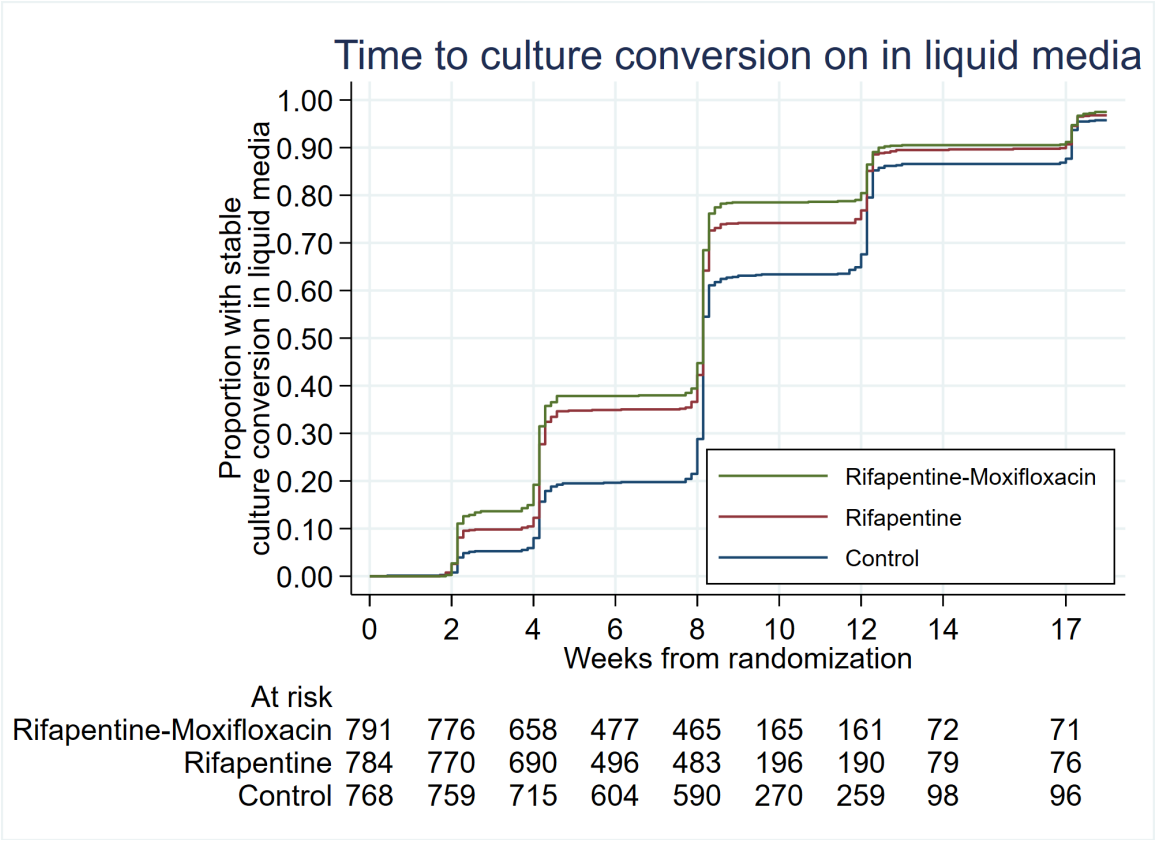


Table S6. Analysis of time to culture conversion on solid media: microbiologically eligible analysis population

Statistic	Control (2RHZE/4RH)	Rifapentine-moxifloxacin (2PHZM/2PHM)	Rifapentine (2PHZE/2PH)
25th centile, weeks	4.14	2.43	4.00
Median (50th centile), weeks	8.14	4.14	4.29
75th centile, weeks	8.29	8.14	8.14
% with culture conversion at 8 weeks	83.50%	90.90%	90.70%
% with culture conversion at 12 weeks	94.40%	96.70%	96.00%
Hazard ratio (95% CI)	Reference	1.34 (1.21, 1.49)	1.30 (1.17, 1.44)

*Since scheduled study visits did not necessarily occur exactly at 8 weeks, the proportion with culture conversion at 8 weeks is estimated from the Kaplan-Meier estimator at t = 10 weeks, and the proportion with culture conversion at 12 weeks as t = 14 weeks.

**There was evidence that the proportional hazard assumption was violated for time to culture conversion on liquid and solid media and therefore the hazard ratio should be interpreted with caution as a representative metric of differences between arms.

Figure S7. Analysis of time to culture conversion on solid media: microbiologically eligible analysis population

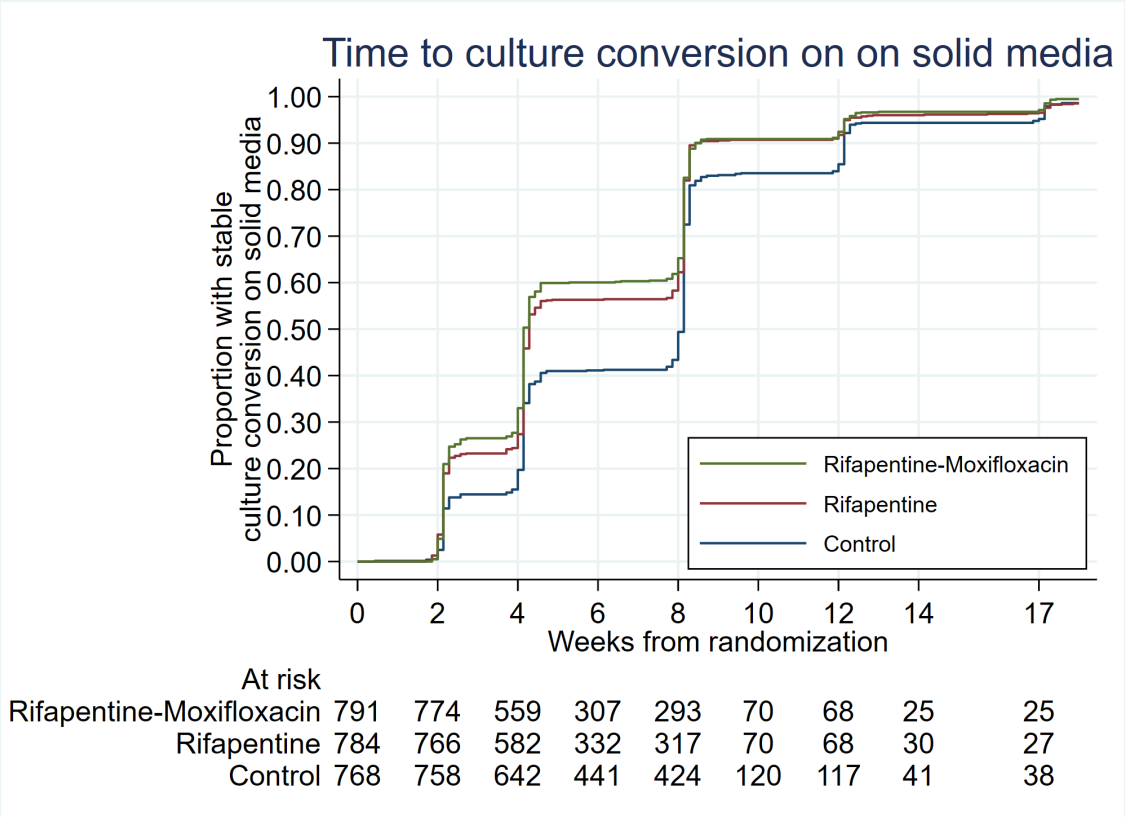


Table S7. Primary safety outcome: numbers of participants experiencing Grade 3 or higher adverse events during treatment (+14 days) by MedDRA preferred term

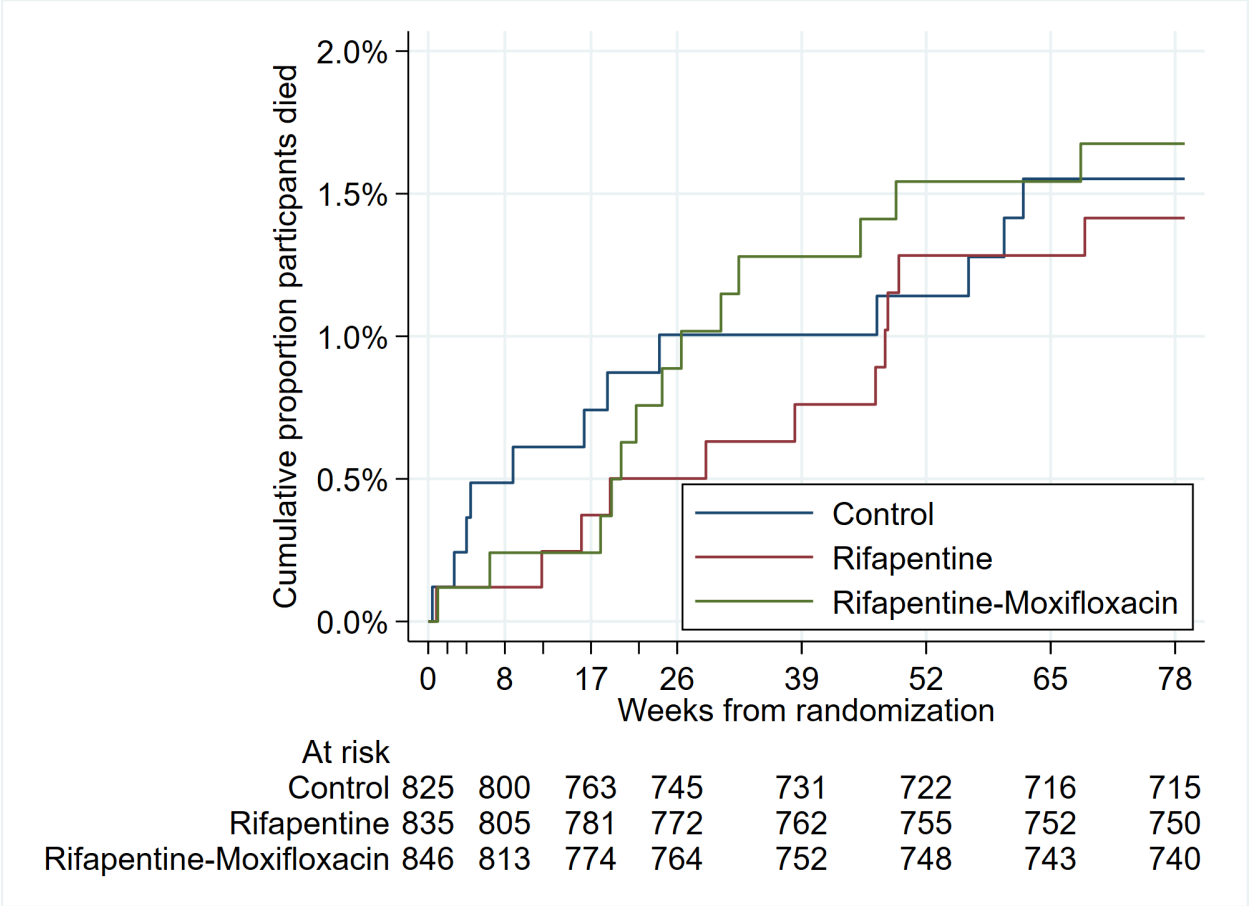
MedDRA preferred term	Control (2RHZE/4RH)	Rifapentine-moxifloxacin (2PHZM/2PHM)	Rifapentine (2PHZE/2PH)	Total
Total in safety population	825	846	835	**2506**
Neutropenia	46 (5.6%)	54 (6.4%)	33 (4.0%)	**133 (5.3%)**
Hepatitis	26 (3.2%)	39 (4.6%)	25 (3.0%)	**90 (3.6%)**
Hypertension	13 (1.6%)	10 (1.2%)	13 (1.6%)	**36 (1.4%)**
Pregnancy	15 (1.8%)	8 (0.9%)	9 (1.1%)	**32 (1.3%)**
Hemoptysis	5 (0.6%)	1 (0.1%)	3 (0.4%)	**9 (0.4%)**
Anemia	3 (0.4%)	4 (0.5%)	1 (0.1%)	**8 (0.3%)**
Diabetes mellitus inadequate control	3 (0.4%)	3 (0.4%)	2 (0.2%)	**8 (0.3%)**
Urticaria	0	4 (0.5%)	1 (0.1%)	**5 (0.2%)**
Pneumonia	1 (0.1%)	3 (0.4%)	1 (0.1%)	**5 (0.2%)**

Pneumonia bacterial	2 (0.2%)	1 (0.1%)	2 (0.2%)	**5 (0.2%)**
Deep vein thrombosis	3 (0.4%)	1 (0.1%)	1 (0.1%)	**5 (0.2%)**
Malaria	3 (0.4%)	2 (0.2%)	0	**5 (0.2%)**
Hyperkalemia	3 (0.4%)	2 (0.2%)	0	**5 (0.2%)**
Blood pressure increased	1 (0.1%)	2 (0.2%)	2 (0.2%)	**5 (0.2%)**
Hyperglycemia	1 (0.1%)	1 (0.1%)	1 (0.1%)	**3 (0.1%)**
Pulmonary embolism	2 (0.2%)	0	1 (0.1%)	**3 (0.1%)**
Leukopenia	0	1 (0.1%)	2 (0.2%)	**3 (0.1%)**
Arthralgia	2 (0.2%)	1 (0.1%)	0	**3 (0.1%)**
Death	1 (0.1%)	0	1 (0.1%)	**2 (0.1%)**
Lymphopenia	0	2 (0.2%)	0	**2 (0.1%)**
Overdose	1 (0.1%)	0	1 (0.1%)	**2 (0.1%)**
Visual acuity reduced	2 (0.2%)	0	0	**2 (0.1%)**
Syncope	0	2 (0.2%)	0	**2 (0.1%)**
Suicide attempt	0	1 (0.1%)	1 (0.1%)	**2 (0.1%)**
Adverse drug reaction	0	2 (0.2%)	0	**2 (0.1%)**
Stab wound	0	0	2 (0.2%)	**2 (0.1%)**
Pregnancy test false positive	1 (0.1%)	0	1 (0.1%)	**2 (0.1%)**
Pelvic inflammatory disease	2 (0.2%)	0	0	**2 (0.1%)**
Rash generalized	0	1 (0.1%)	1 (0.1%)	**2 (0.1%)**
Pruritis	0	1 (0.1%)	1 (0.1%)	**2 (0.1%)**
Rash pruritic	0	0	2 (0.2%)	**2 (0.1%)**
Pseudohyperkalemia	1 (0.1%)	1 (0.1%)	0	**2 (0.1%)**
Hypoalbuminemia	0	0	2 (0.2%)	**2 (0.1%)**
Urinary tract infection	1 (0.1%)	0	1 (0.1%)	**2 (0.1%)**
Any grade 3-5 adverse event	**159 (19.3%)**	**159 (18.8%)**	**119 (14.3%)**	**437 (17.4%)**

Table S8. Mortality during treatment and follow-up

Description	**Control (2RHZE/4RH)**	**Rifapentine-moxifloxacin (2PHZM/2PHM)**	**Rifapentine (2PHZE/2PH)**	**Total**
Total randomized	**829**	**849**	**838**	**2516**
Total in safety analysis population	**825**	**846**	**835**	**2506**
Death during study treatment (up to 14 days after the last study dose)	7 (0.8%)	3 (0.4%)	4 (0.5%)	14 (0.6%)
TB-related	6 (0.7%)	2 (0.2%)	1 (0.1%)	9 (0.4%)
All deaths during treatment and follow-up	12 (1.4%)	13 (1.5%)	11 (1.3%)	36 (1.4%)
TB-related	8 (1.0%)	3 (0.4%)	4 (0.5%)	15 (0.6%)

Figure S8. Time to All-cause mortality during treatment and follow-up



At risk								
Control	825	800	763	745	731	722	716	715
Rifapentine	835	805	781	772	762	755	752	750
Rifapentine-Moxifloxacin	846	813	774	764	752	748	743	740

Table S9. Deaths during study treatment, up to 14 days after last study dose, by MedDRA Preferred Term

Control (2RHZE/4RH)	Rifapentine-moxifloxacin (2PHZM/2PHM)	Rifapentine (2PHZE/2PH)
1 Paracoccidioides infection 1 sepsis 1 papillary thyroid cancer 1 central nervous system lesion 1 hemoptysis 1 pulmonary embolism 1 death	1 thrombotic thrombocytopenic purpura* 1 cardiac failure congestive 1 pulmonary tuberculosis	1 alcohol poisoning 1 road traffic accident 1 pulmonary embolism 1 death
7 (0.8%)	**3 (0.4%)**	**4 (0.5%)**

*****suspected unexpected serious adverse reaction

Table S10. Deaths > 14 days after last study dose, by MedDRA Preferred Term

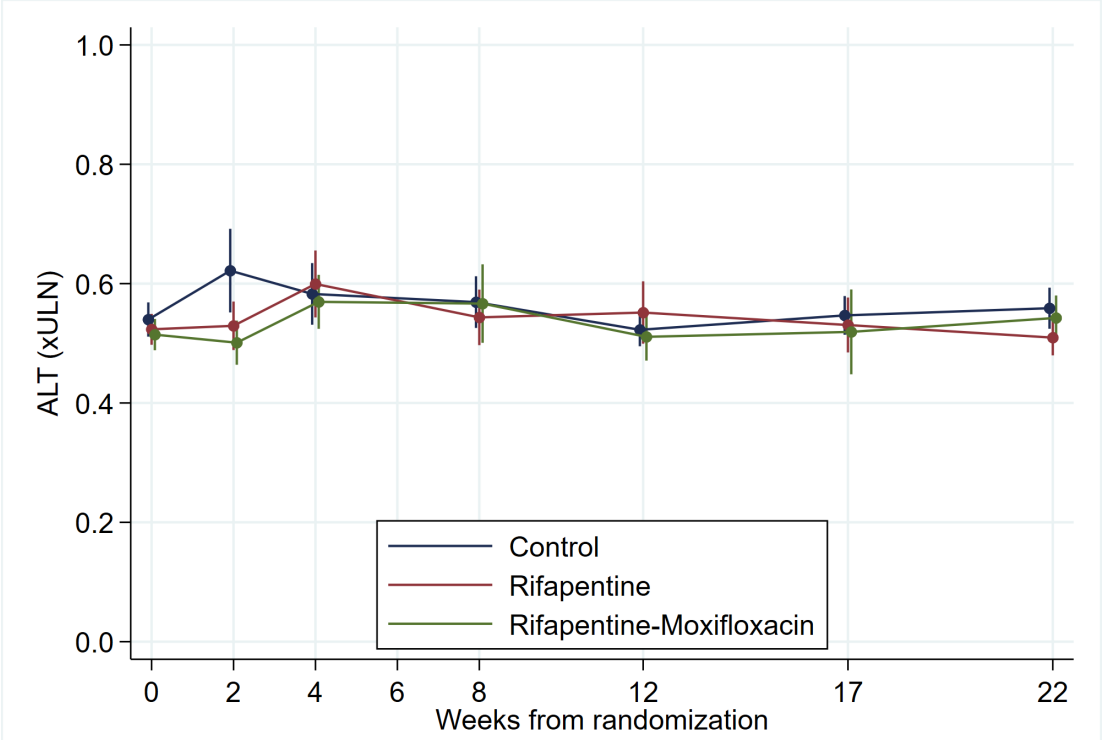
Control (2RHZE/4RH)	Rifapentine-moxifloxacin (2PHZM/2PHM)	Rifapentine (2PHZE/2PH)
1 sudden death 1 neoplasm malignant 1 dyspnea 1 pulmonary mass 1 death	1 right ventricular failure 1 hepatitis 1 gunshot wound 2 road traffic accident 1 esophageal carcinoma 1 squamous cell carcinoma 1 pneumothorax 1 pulmonary embolism 1 death	1 alcoholic liver disease 1 lower respiratory tract infection 1 pulmonary tuberculosis 1 gas poisoning 1 road traffic accident 1 bladder transitional cell carcinoma 1 death
5 (0.6%)	**10 (1.2%)**	**7 (0.8%)**

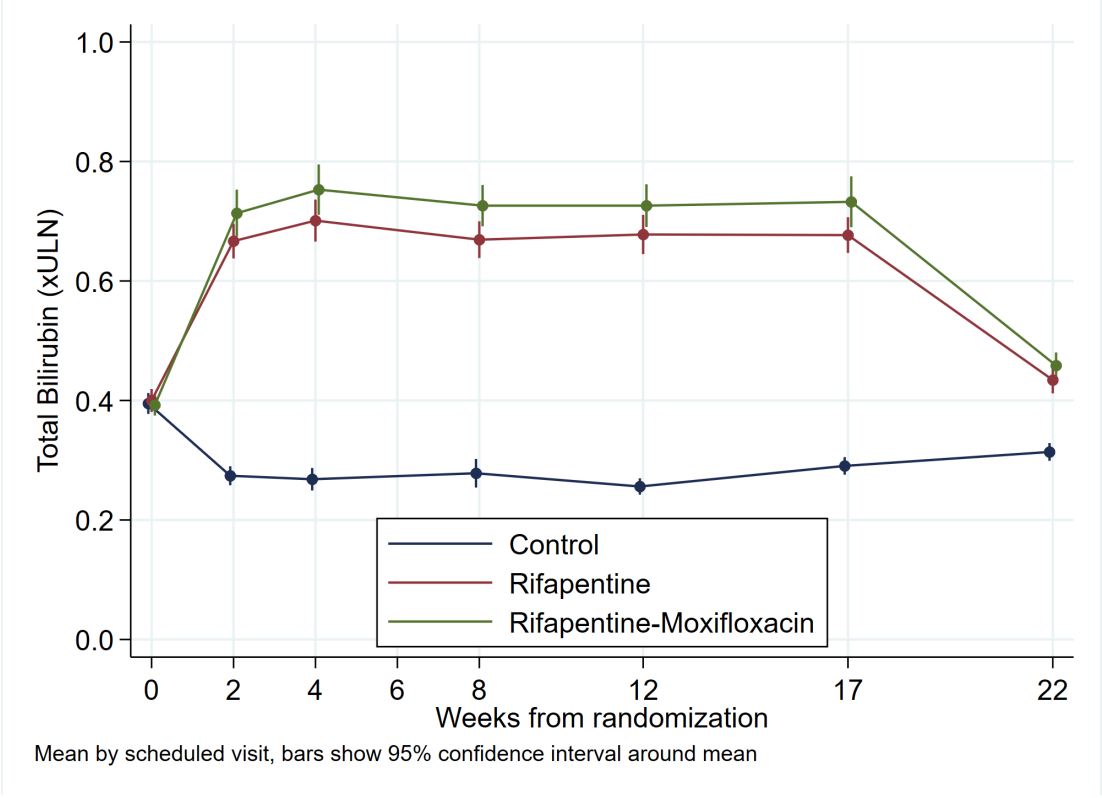
Table S11. Primary Safety Outcome: numbers of participants experiencing grade 3-5 adverse events during treatment (+14 days) by MedDRA system organ class

MedDRA system organ class (SOC)	Control	Rifapentine-Moxifloxacin	Rifapentine	Overall
Total in safety population	**825**	**846**	**835**	**2506**
Blood & lymphatic system disorders	51 (6.2%)	61 (7.2%)	35 (4.2%)	147 (5.9%)
Hepatobiliary disorders	26 (3.2%)	39 (4.6%)	26 (3.1%)	91 (3.6%)
Vascular disorders	17 (2.1%)	12 (1.4%)	14 (1.7%)	43 (1.7%)
Pregnancy, puerperium & perinatal disorders	16 (1.9%)	9 (1.1%)	9 (1.1%)	34 (1.4%)
Infections & infestations	16 (1.9%)	10 (1.2%)	8 (1.0%)	34 (1.4%)
Metabolism & nutrition disorders	11 (1.3%)	9 (1.1%)	6 (0.7%)	26 (1.0%)
Respiratory, thoracic & mediastinal disorders	7 (0.8%)	4 (0.5%)	5 (0.6%)	16 (0.6%)
Injury, poisoning & procedural complications	9 (1.1%)	0	6 (0.7%)	15 (0.6%)
Skin & subcutaneous tissue disorders	1 (0.1%)	6 (0.7%)	6 (0.7%)	13 (0.5%)
Eye disorders	4 (0.5%)	4 (0.5%)	1 (0.1%)	9 (0.4%)
Investigations	3 (0.4%)	3 (0.4%)	3 (0.4%)	9 (0.4%)
Nervous system disorders	3 (0.4%)	5 (0.6%)	1 (0.1%)	9 (0.4%)
Gastrointestinal disorders	3 (0.4%)	2 (0.2%)	1 (0.1%)	6 (0.2%)
Neoplasms benign, malignant & unspecified	4 (0.5%)	1 (0.1%)	1 (0.1%)	6 (0.2%)
General disorders & administration site conditions	3 (0.4%)	2 (0.2%)	1 (0.1%)	6 (0.2%)
Musculoskeletal & connective system disorders	3 (0.4%)	1 (0.1%)	1 (0.1%)	5 (0.2%)
Psychiatric disorders	0	2 (0.2%)	1 (0.1%)	3 (0.1%)
Cardiac disorders	0	3 (0.4%)[1]	0	3 (0.1%)
Renal & urinary disorders	0	2 (0.2%)	0	2 (0.1%)
Immune system disorders	0	1 (0.1%)	0	1 (0.1%)
Any grade 3-5 adverse event	**159 (19.3%)**	**159 (18.8%)**	**119 (14.3%)**	**437 (17.4%)**

[1]One participant with congestive cardiac failure; one participant with right ventricular failure; one participant with reported palpitations and borderline QTcF prolongation to 461 msec from 402 msec prior to study treatment (change of 59 msec).

Figure S9. Graph of mean values over time for blood alanine aminotransferase (top) and blood total bilirubin (bottom) among participants in the safety analysis population





4 Additional tables and figures

Figure S10. Recruitment by country

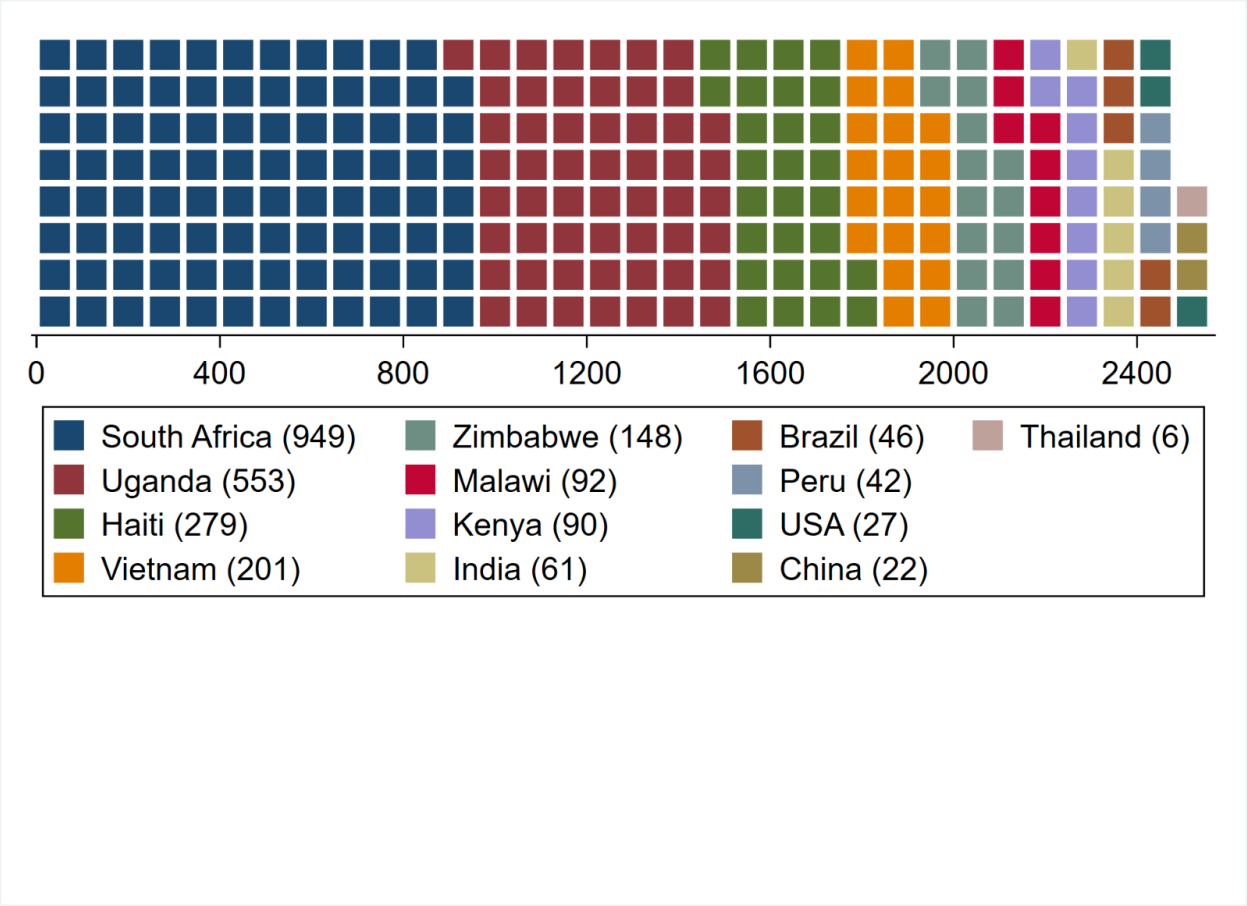


Table S12. Characteristics of the participants at baseline (assessable analysis population)

Characteristic	Control	Rifapentine-Moxifloxacin	Rifapentine	Overall
Total in assessable analysis population	**726**	**756**	**752**	**2234**
Male sex – no. (%)	515 (71)	539 (71)	541 (72)	1595 (71)
Age – median	31.0	31.1	30.9	31.0
Age group – no. (%)				
12-17 years	19 (3)	25 (3)	18 (2)	62 (3)
18-35 years	447 (62)	464 (61)	467 (62)	1378 (62)
>35 years	260 (36)	267 (35)	267 (36)	794 (36)
Race – no. (%)*				
Asian	83 (11)	85 (11)	91 (12)	259 (12)
Black or African American	520 (72)	526 (70)	546 (73)	1592 (71)
White	13 (2)	13 (2)	7 (1)	33 (2)
More than one race	107 (15)	131 (17)	107 (14)	345 (15)
HIV-positive – no. (%)	59 (8)	58 (8)	65 (9)	182 (8)
CD4 among those HIV positive – median (IQR)	331 (208-466)	352 (219-465)	366 (221-440)	344 (220-455)
Cavitation on baseline chest X-ray – no. (%)				
Absent	194 (27%)	203 (27%)	196 (26%)	593 (27%)
<4cm	233 (32%)	261 (35%)	237 (32%)	731 (33%)
≥4cm	295 (41%)	286 (38%)	314 (42%)	895 (40%)
Weight in kg – median	52.7	53.0	53.3	53.0
Body mass index, kg/m^2 – median	18.9	19.0	18.9	18.9
Current smoker – no. (%)	187 (26)	163 (22)	192 (26)	542 (24)
8^{th} grade education or less – no. (%)	209 (29)	211 (28)	213 (28)	633 (28)
Prior tuberculosis treatment – no. (%)	80 (11)	93 (12)	78 (10)	251 (11)
*Race was reported by trial participants; information about race was not available for 5 participants.				

Table S13. Summary of retention during follow-up

Visit	Status	Control	Rifapentine-Moxifloxacin	Rifapentine	Overall
	Total in population	**768**	**791**	**784**	**2343**
Month 9	**Seen here or later**	**725 (94.4%)**	**749 (94.7%)**	**747 (95.3%)**	**2221 (94.8%)**
	Died	8 (1.0%)	11 (1.4%)	9 (1.1%)	28 (1.2%)
	Not seen	6 (0.8%)	6 (0.8%)	4 (0.5%)	16 (0.7%)
	Discontinued study	29 (3.8%)	25 (3.2%)	24 (3.1%)	78 (3.3%)
Month 12	**Seen here or later**	**717 (93.4%)**	**747 (94.4%)**	**745 (95.0%)**	**2209 (94.3%)**
	Died	11 (1.4%)	12 (1.5%)	9 (1.1%)	32 (1.4%)
	Not seen	9 (1.2%)	6 (0.8%)	4 (0.5%)	19 (0.8%)
	Discontinued study	31 (4.0%)	26 (3.3%)	26 (3.3%)	83 (3.5%)
Month 15	**Seen here or later**	**713 (92.8%)**	**745 (94.2%)**	**742 (94.6%)**	**2200 (93.9%)**
	Died	11 (1.4%)	13 (1.6%)	10 (1.3%)	34 (1.5%)
	Not seen	10 (1.3%)	6 (0.8%)	5 (0.6%)	21 (0.9%)
	Discontinued study	34 (4.4%)	27 (3.4%)	27 (3.4%)	88 (3.8%)
Month 18	**Seen here or later**	**709 (92.3%)**	**739 (93.4%)**	**736 (93.9%)**	**2184 (93.2%)**
	Died	11 (1.4%)	13 (1.6%)	10 (1.3%)	34 (1.5%)
	Not seen	0	1 (0.1%)	2 (0.3%)	3 (0.1%)
	Discontinued study	48 (6.3%)	38 (4.8%)	36 (4.6%)	122 (5.2%)

Figure S11. Safety summary: participants with adverse events with onset during study treatment (up to 14 days after the last study dose)

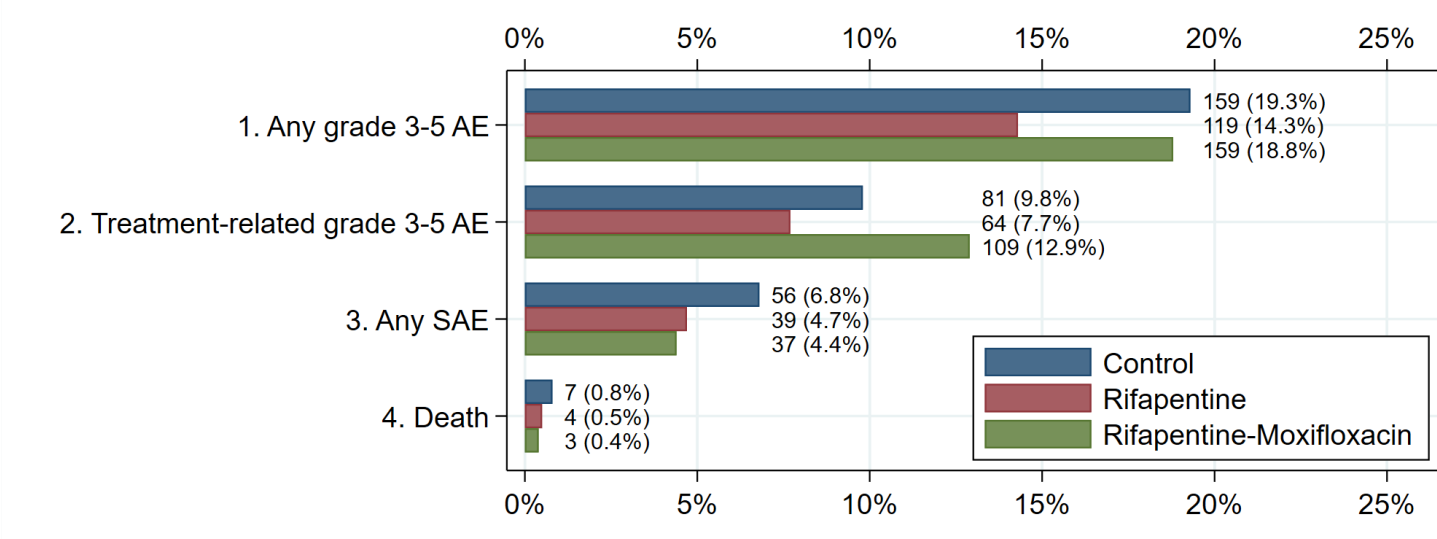


Figure S12. Safety summary: participants with adverse events up to 28 weeks after randomization

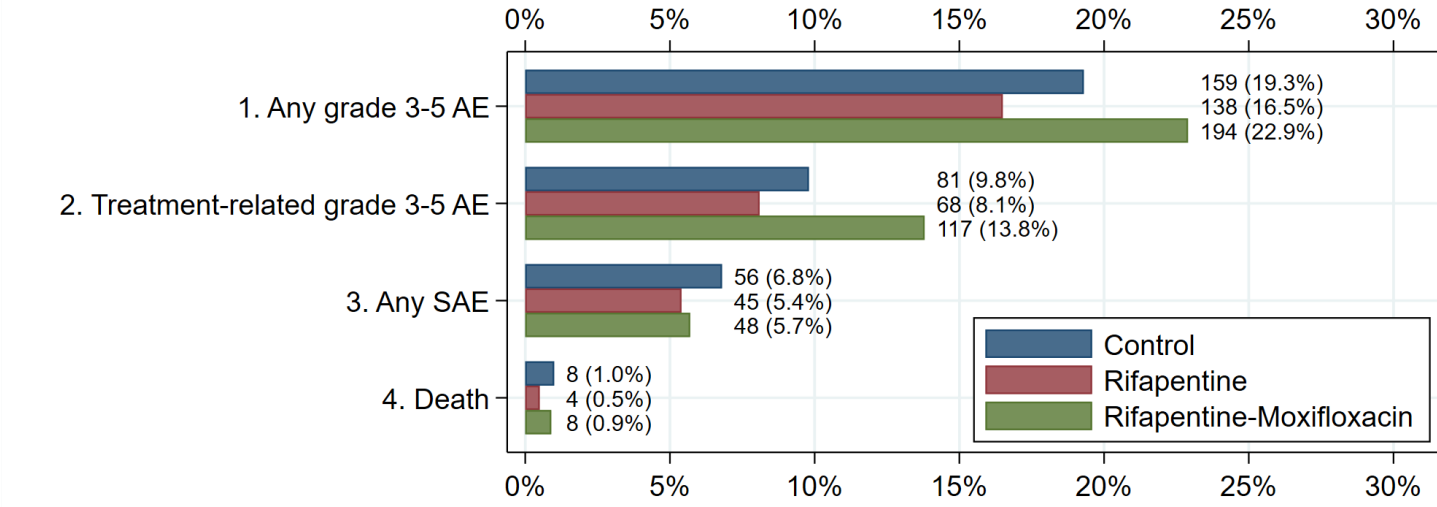
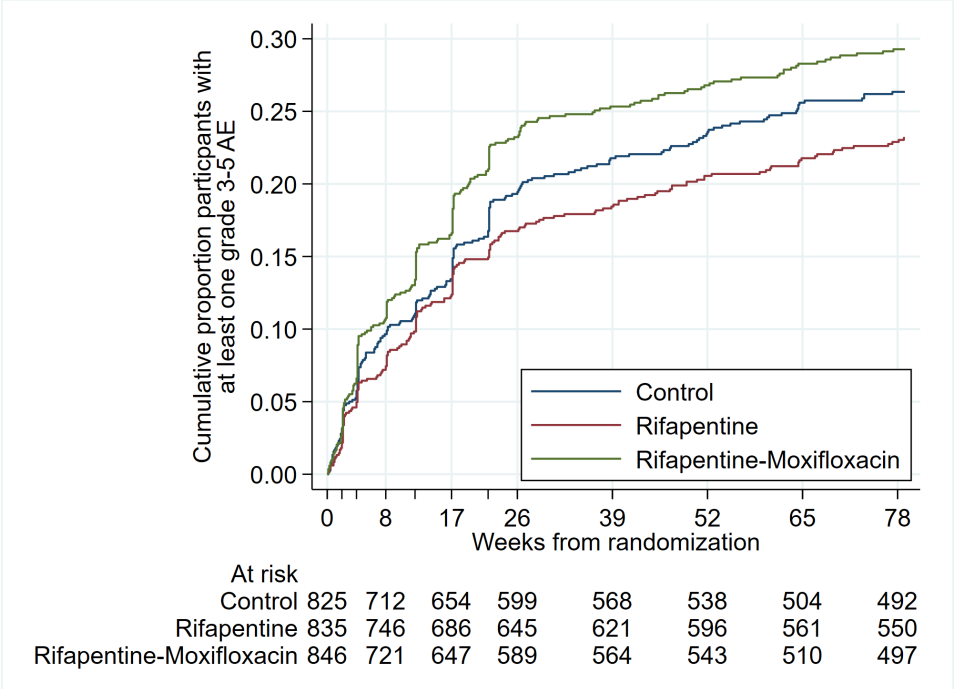
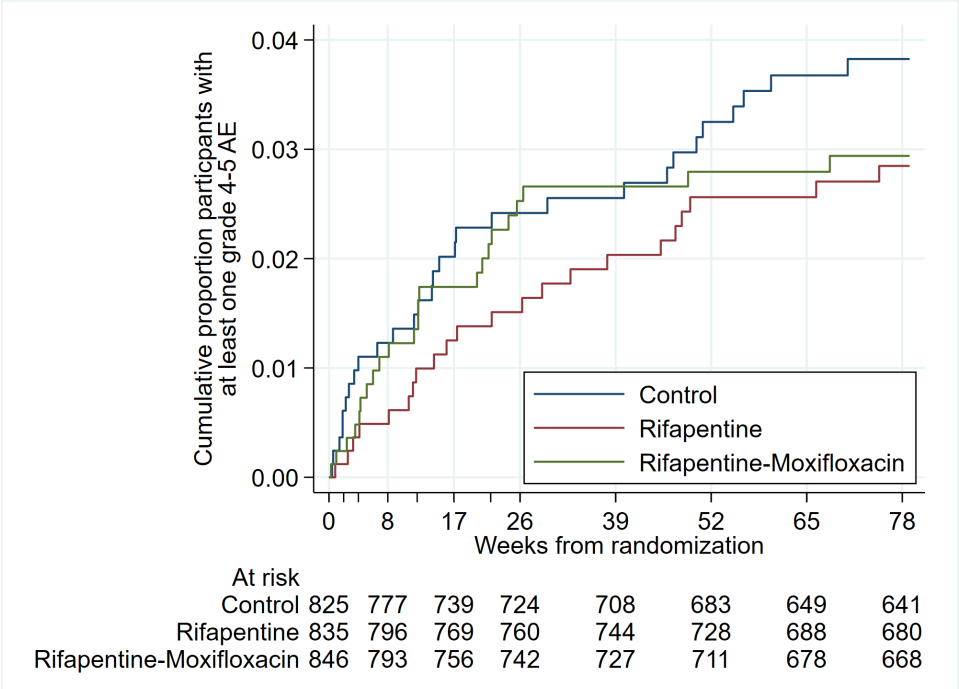


Figure S13. Analysis of time to first all-cause grade 3-5 adverse events during treatment and follow-up



At risk								
Control	825	712	654	599	568	538	504	492
Rifapentine	835	746	686	645	621	596	561	550
Rifapentine-Moxifloxacin	846	721	647	589	564	543	510	497

Figure S14. Analysis of time to first all-cause grade 4-5 adverse events during treatment and follow-up



At risk								
Control	825	777	739	724	708	683	649	641
Rifapentine	835	796	769	760	744	728	688	680
Rifapentine-Moxifloxacin	846	793	756	742	727	711	678	668

Table S14. Summary of time to first all-cause grade 3-5, grade 4-5, grade 5 adverse events during treatment and follow-up:

Hazard ratio (95% CI)	Rifapentine-moxifloxacin vs. Control	Rifapentine vs. Control
Time to first Grade 3-5 adverse event	1.15 (0.95, 1.38)	0.86 (0.70, 1.05)
Time to first grade 4-5 adverse event	0.77 (0.45, 1.33)	0.73 (0.42, 1.27)
Time to death (grade 5 adverse event)	1.06 (0.48, 2.32)	0.88 (0.39, 2.00)

Note. There was no evidence that the proportional hazard assumption was violated for any of these analyses.

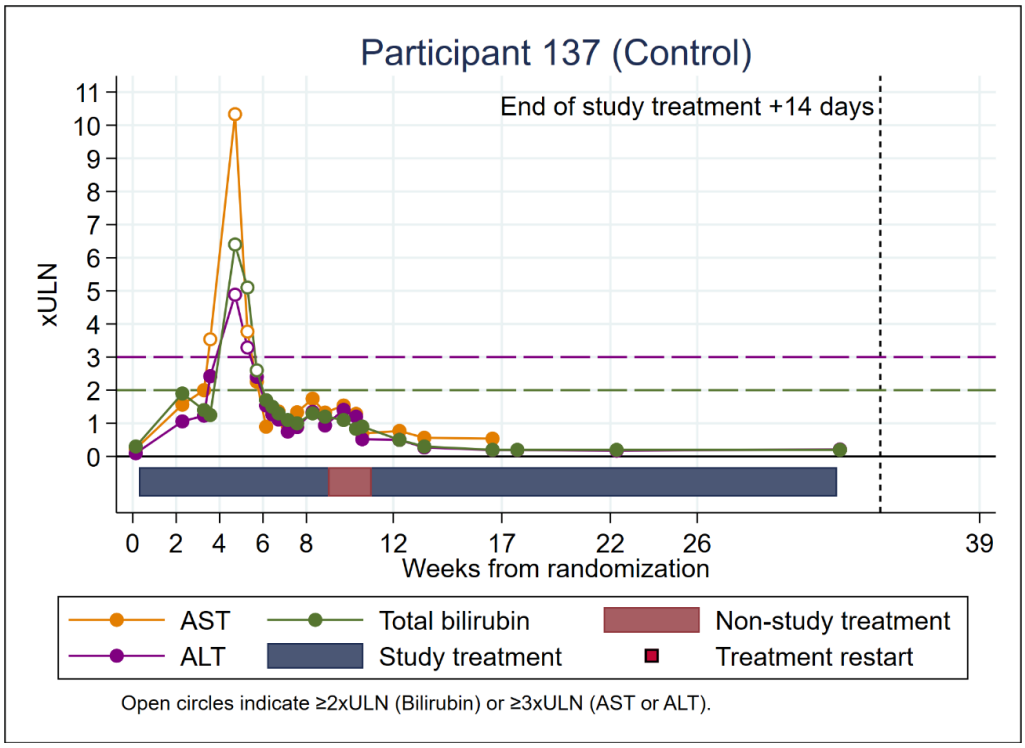
Table S15. Numbers of serious adverse events (SAEs) reported during treatment (+14 days) by MedDRA system organ class

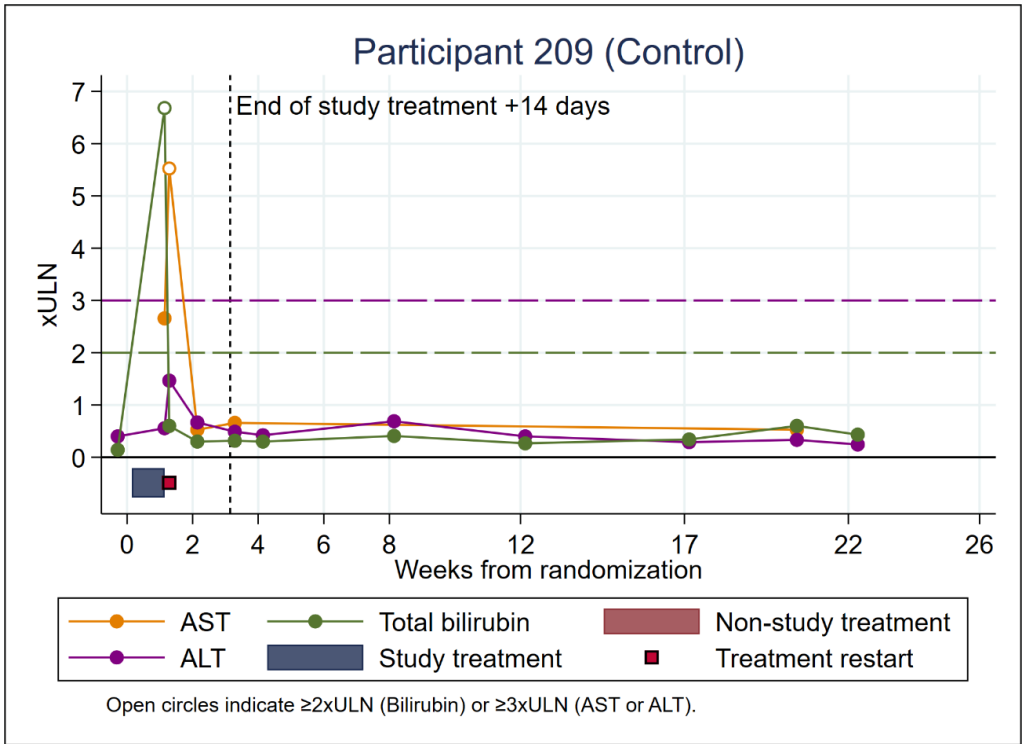
MedDRA system organ class (SOC)	Control	Rifapentine	Rifapentine-Moxifloxacin	Overall
Total in safety population	**825**	**835**	**846**	**2506**
Hepatobiliary Disorders	10 (1.2%)	5 (0.6%)	7 (0.8%)	**22 (0.9%)**
Injury, Poisoning & Procedural Complications	8 (1.0%)	8 (1.0%)	0	**16 (0.6%)**
Respiratory, Thoracic & Mediastinal Disorders	7 (0.8%)	5 (0.6%)	3 (0.4%)	**15 (0.6%)**
Infections & Infestations	5 (0.6%)	5 (0.6%)	5 (0.6%)	**15 (0.6%)**
Blood & Lymphatic System Disorders	3 (0.4%)	2 (0.2%)	5 (0.6%)	**10 (0.4%)**
Pregnancy, Puerperium & Perinatal Conditions	3 (0.4%)	3 (0.4%)	3 (0.4%)	**9 (0.4%)**
Skin & Subcutaneous Tissue Disorders	0	3 (0.4%)	5 (0.6%)	**8 (0.3%)**
Vascular Disorders	4 (0.5%)	2 (0.2%)	1 (0.1%)	**7 (0.3%)**
Nervous System Disorders	3 (0.4%)	0	3 (0.4%)	**6 (0.2%)**
Neoplasms Benign, Malignant & Unspecified (Incl Cysts & Polyps)	4 (0.5%)	1 (0.1%)	1 (0.1%)	**6 (0.2%)**
Gastrointestinal Disorders	4 (0.5%)	1 (0.1%)	0	**5 (0.2%)**
Metabolism & Nutrition Disorders	2 (0.2%)	1 (0.1%)	1 (0.1%)	**4 (0.2%)**
General Disorders & Administration Site Conditions	2 (0.2%)	1 (0.1%)	1 (0.1%)	**4 (0.2%)**
Cardiac Disorders	0	1 (0.1%)	3 (0.4%)	**4 (0.2%)**
Psychiatric Disorders	0	1 (0.1%)	2 (0.2%)	**3 (0.1%)**
Musculoskeletal & Connective Tissue Disorders	2 (0.2%)	0	0	**2 (0.1%)**
Renal & Urinary Disorders	0	0	2 (0.2%)	**2 (0.1%)**
Eye Disorders	1 (0.1%)	0	0	**1 (0.0%)**
Any SAE	**56 (6.8%)**	**39 (4.7%)**	**37 (4.4%)**	**132 (5.3%)**

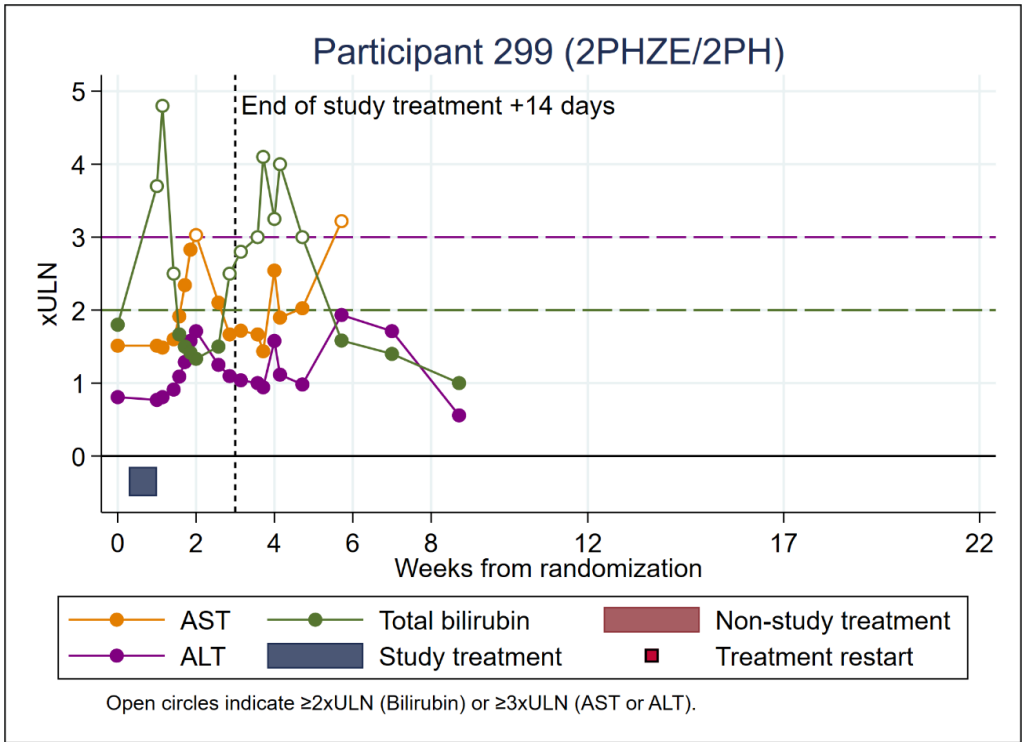
[1] One participant hospitalized with grade 2 myocardial ischemia

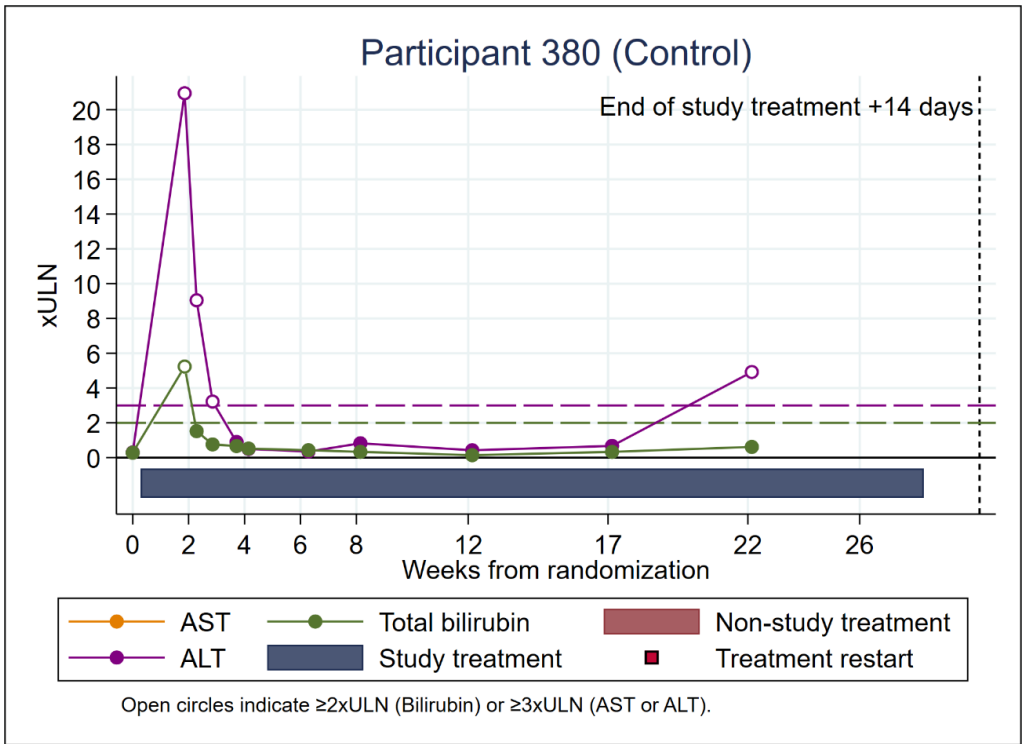
[2] One participant with two episodes of congestive cardiac failure, one participant with right ventricular failure, and one participant with reported palpitations and borderline QTcF prolongation to 461 msec from 402 msec prior to study treatment (change of 59 msec).

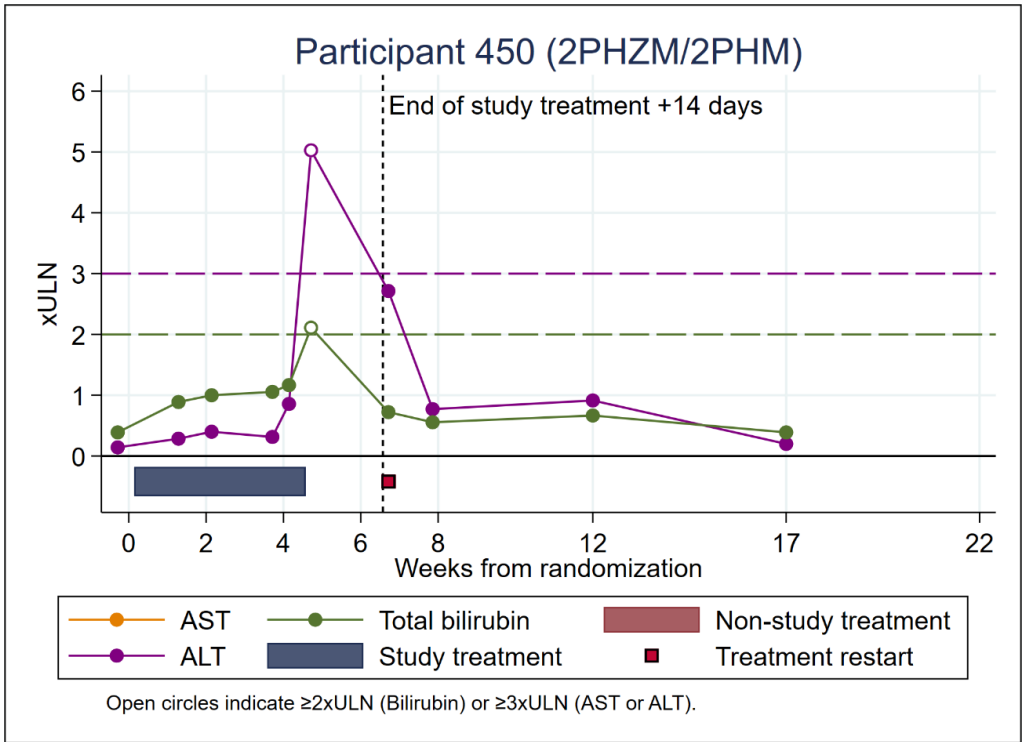
Figure S16. Safety laboratory parameters for 25 participants that met Hy's Law during study treatment and up to 14 days after the last dose of study medications.

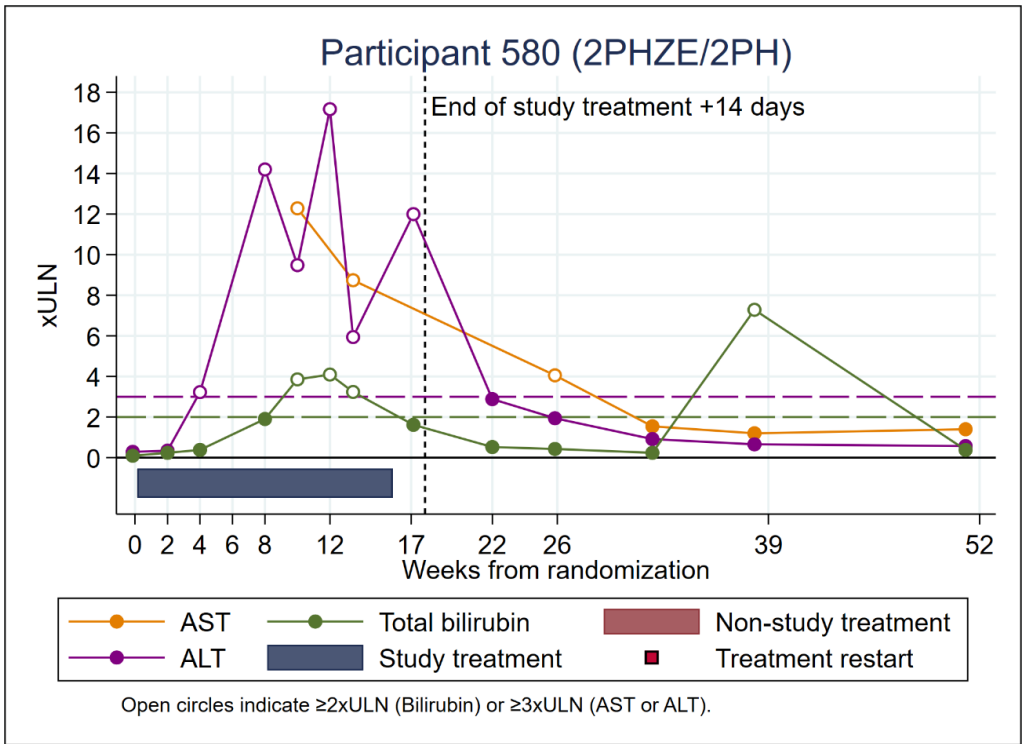


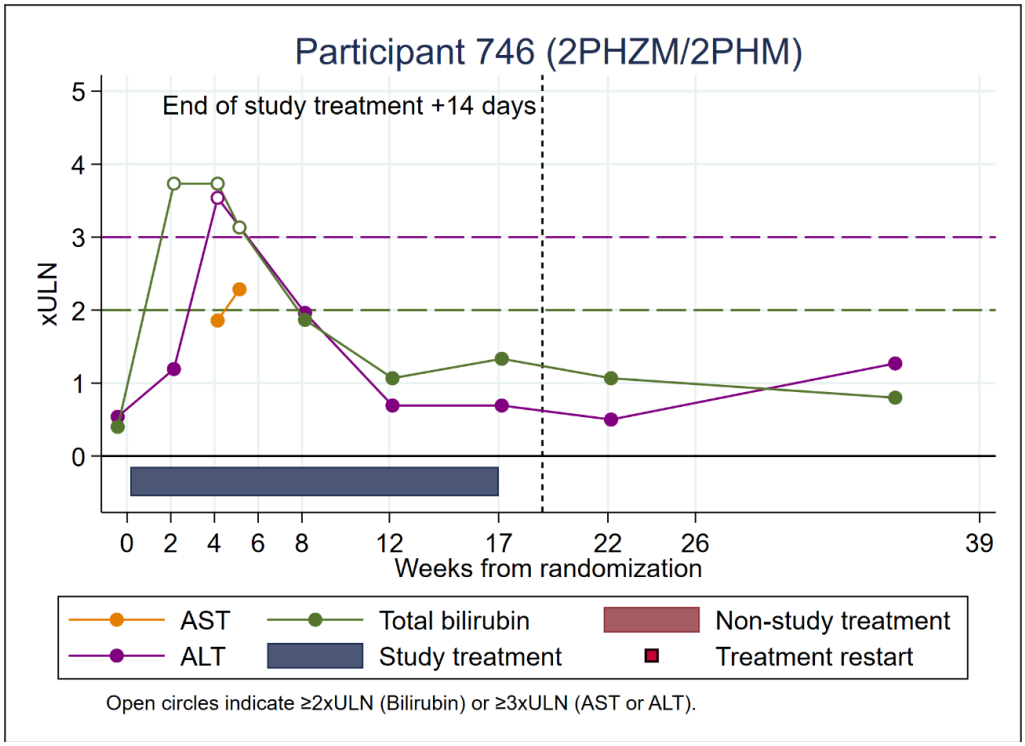


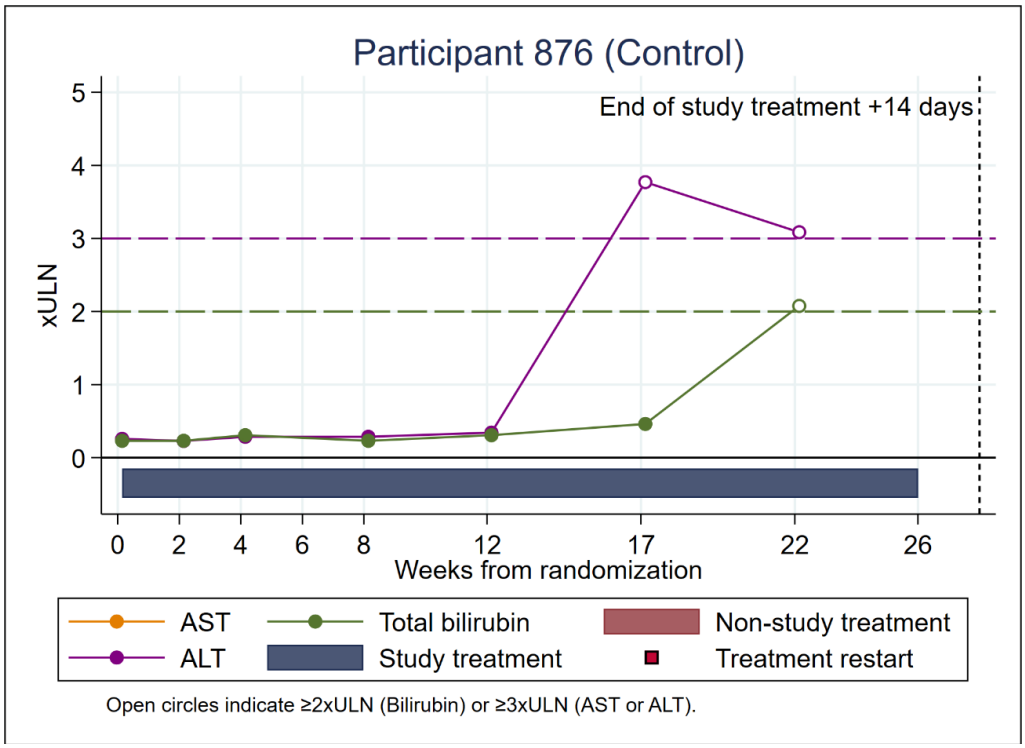

Participant 299 (2PHZE/2PH)
End of study treatment +14 days
xULN
0
1
2
3
4
5
0
2
4
6
8
12
17
22
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

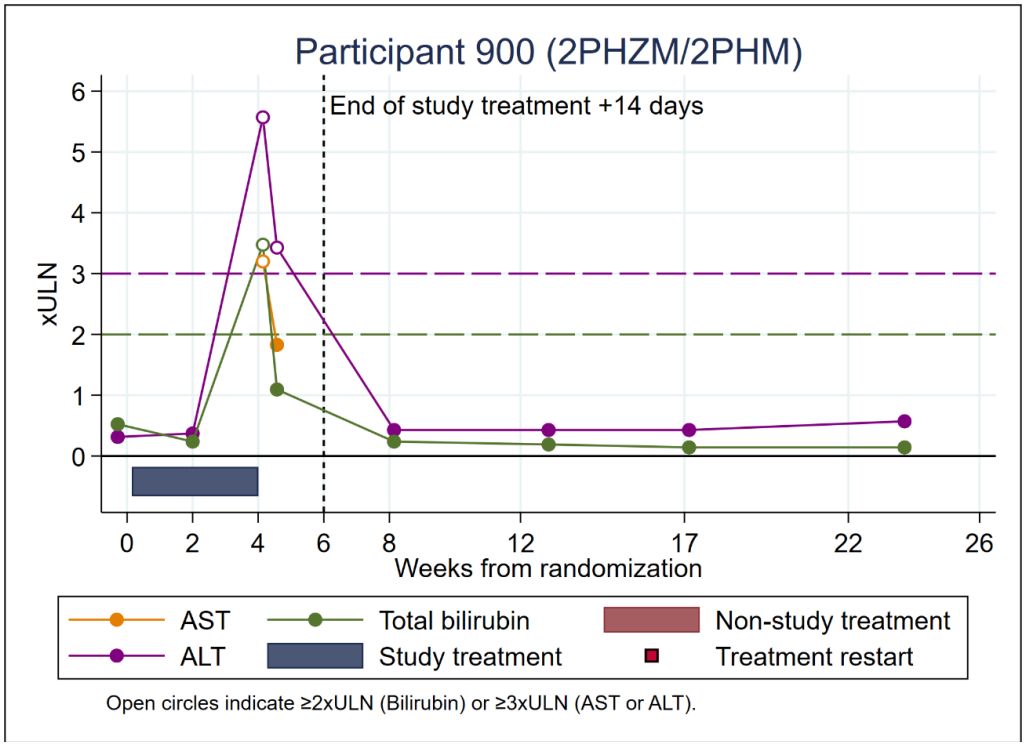

Participant 380 (Control)
End of study treatment +14 days
xULN
0
2
4
6
8
10
12
14
16
18
20
0
2
4
6
8
12
17
22
26
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

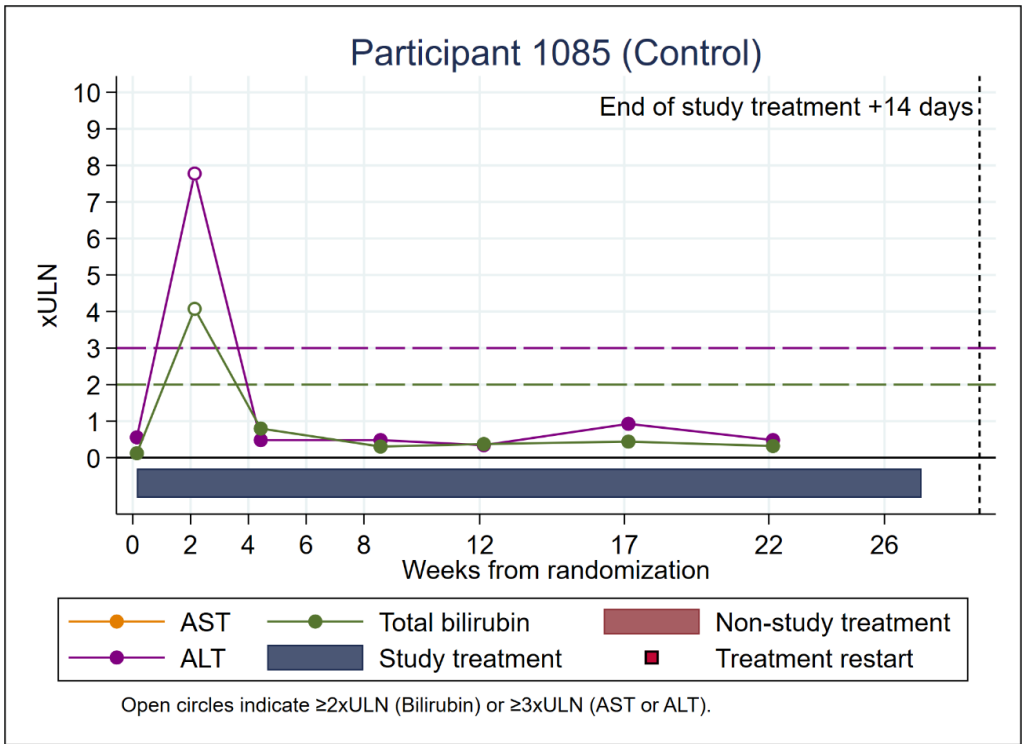

Participant 450 (2PHZM/2PHM)
End of study treatment +14 days
xULN
0
1
2
3
4
5
6
0
2
4
6
8
12
17
22
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

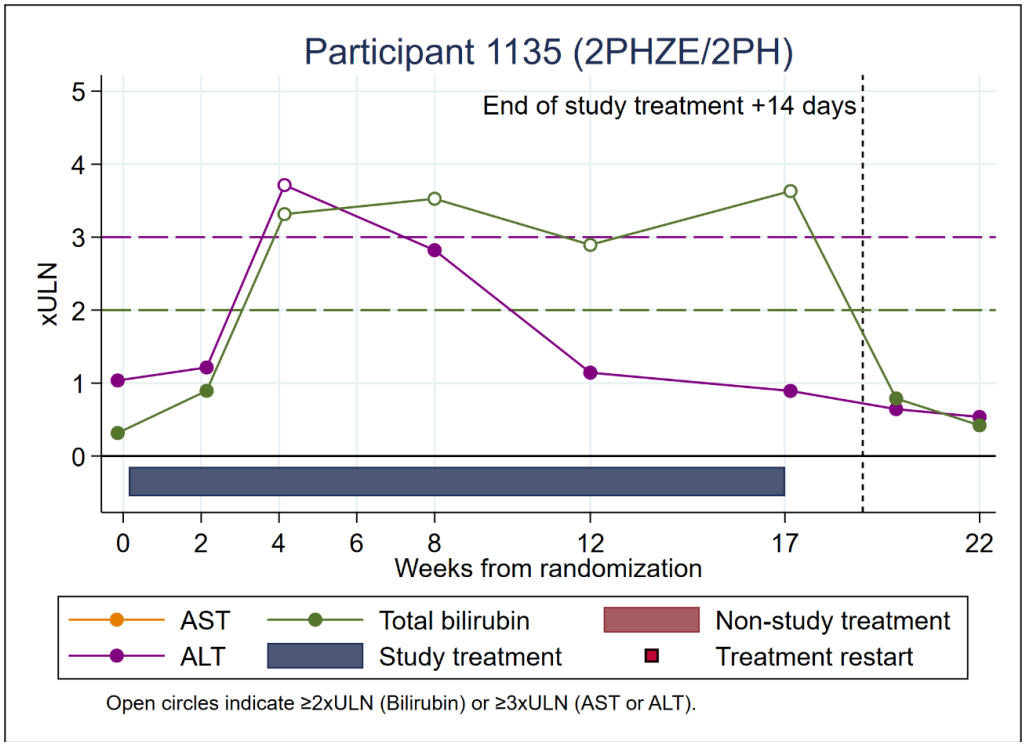

Participant 580 (2PHZE/2PH)
End of study treatment +14 days
xULN
0
2
4
6
8
10
12
14
16
18
0
2
4
6
8
12
17
22
26
39
52
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

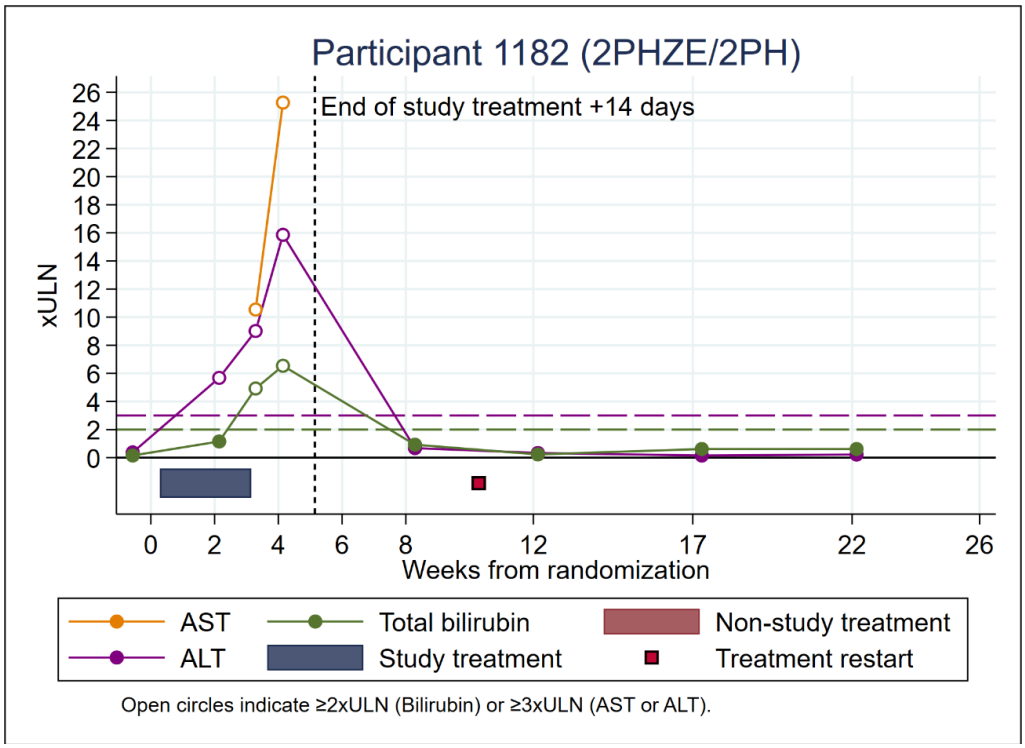

Participant 746 (2PHZM/2PHM)
End of study treatment +14 days
xULN
0
1
2
3
4
5
0 2 4 6 8 12 17 22 26 39
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

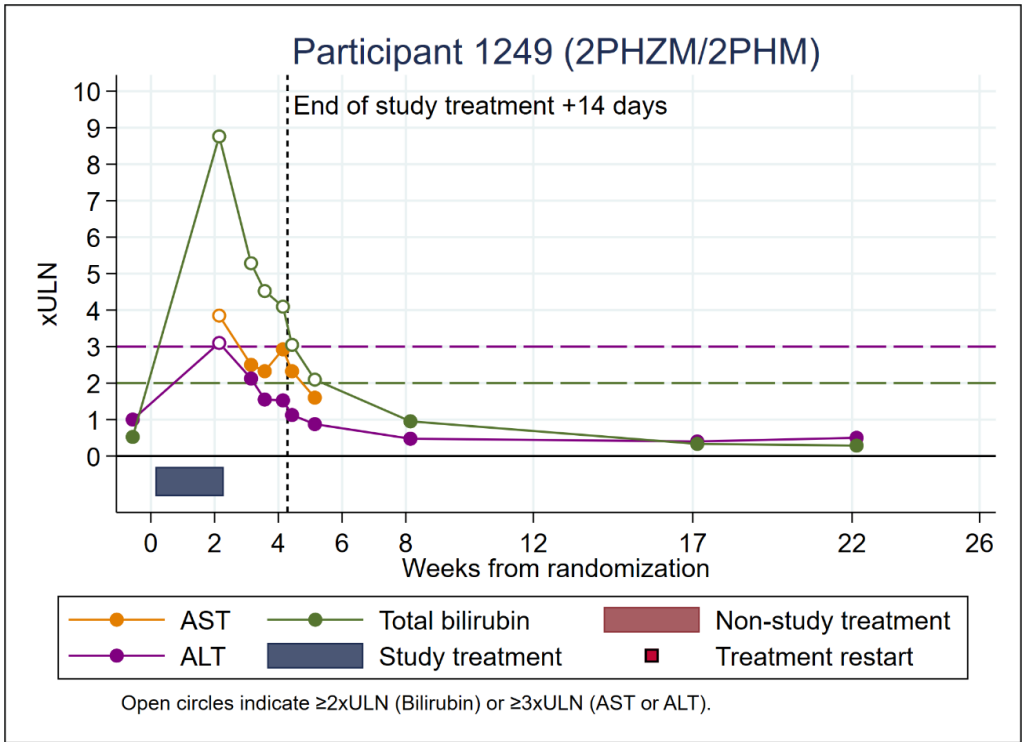

Participant 876 (Control)
End of study treatment +14 days
xULN
0
1
2
3
4
5
0 2 4 6 8 12 17 22 26
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

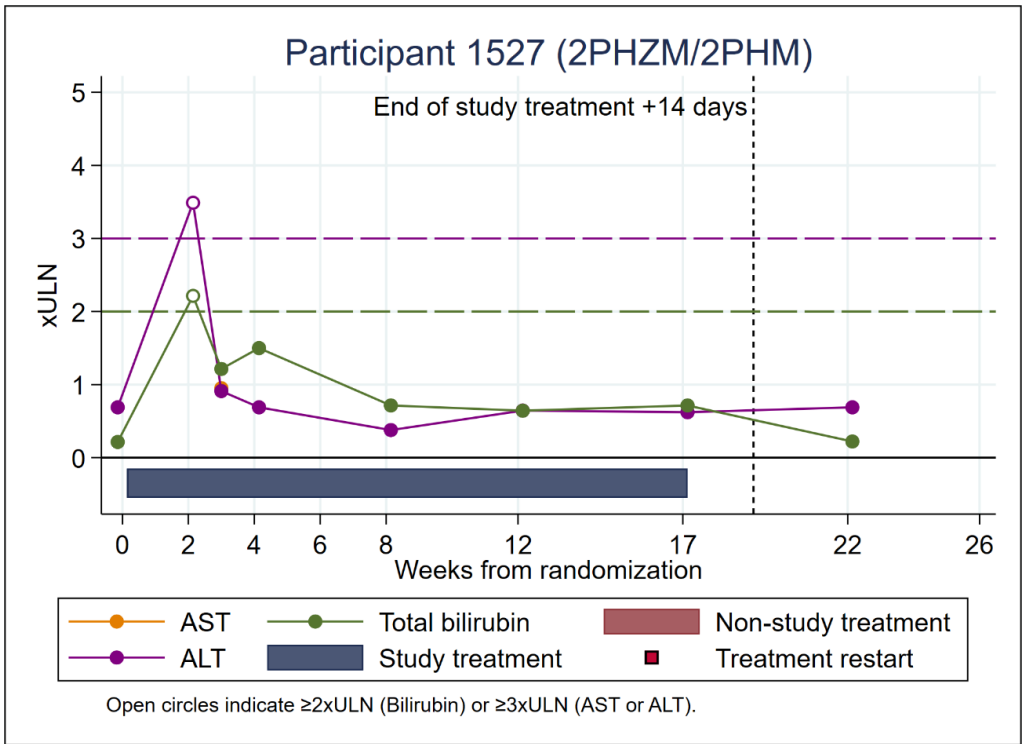

Participant 900 (2PHZM/2PHM)
End of study treatment +14 days
xULN
0
1
2
3
4
5
6
0
2
4
6
8
12
17
22
26
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

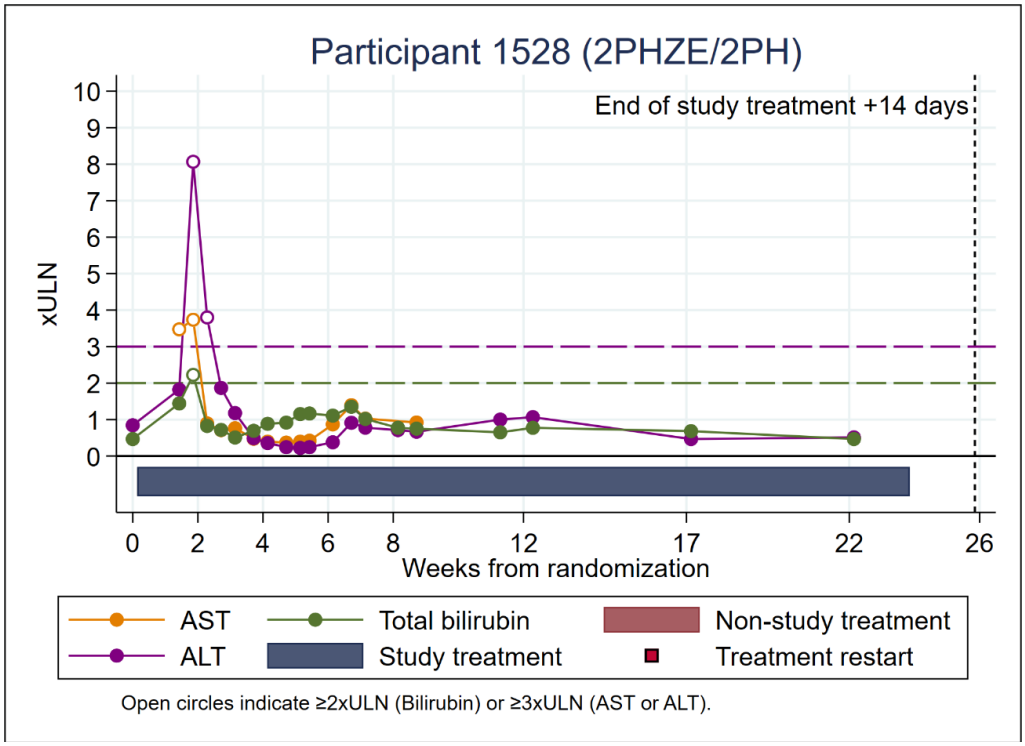

Participant 1085 (Control)
End of study treatment +14 days
xULN
0
1
2
3
4
5
6
7
8
9
10
0
2
4
6
8
12
17
22
26
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

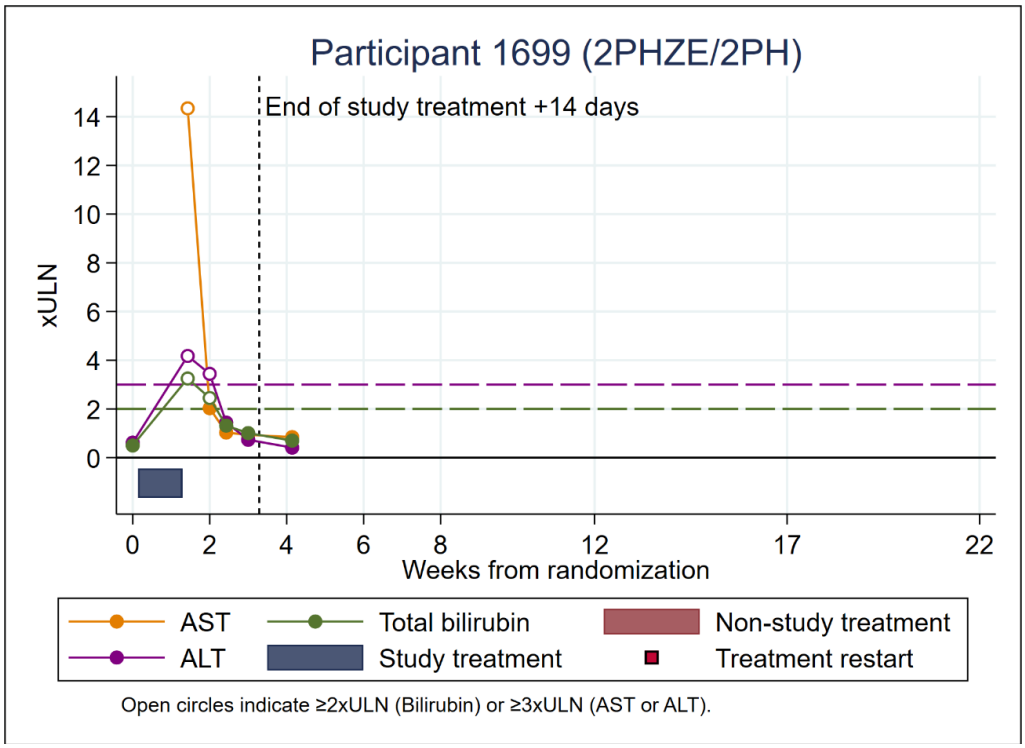

Participant 1135 (2PHZE/2PH)
End of study treatment +14 days
xULN
0
1
2
3
4
5
0
2
4
6
8
12
17
22
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

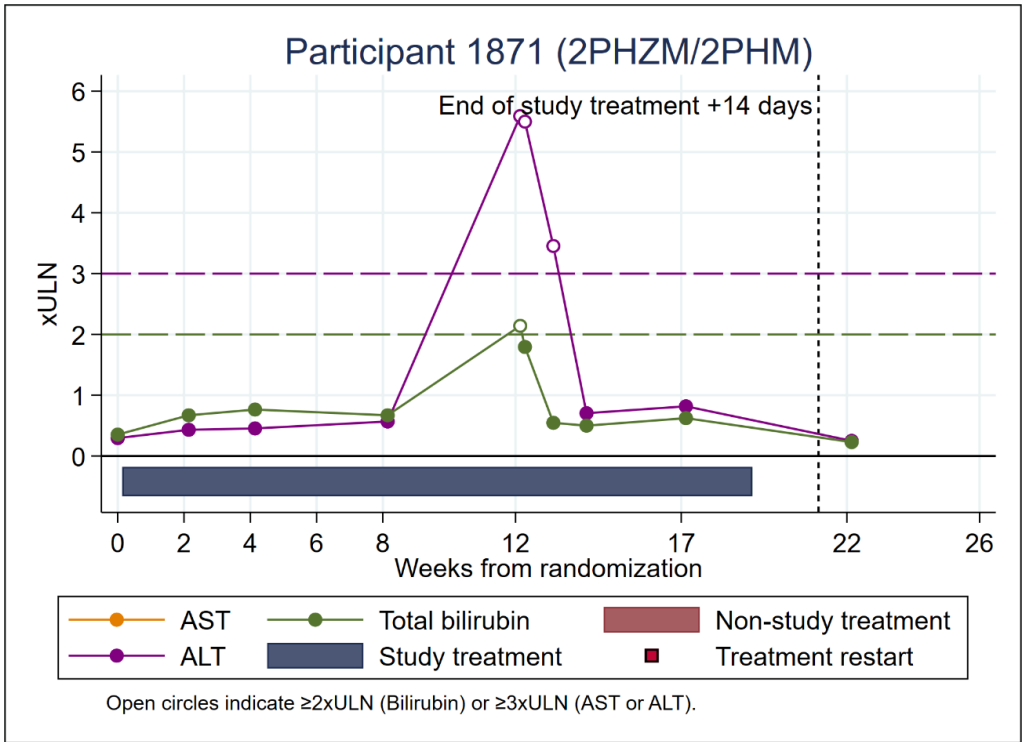

Participant 1182 (2PHZE/2PH)
End of study treatment +14 days
xULN
0
2
4
6
8
10
12
14
16
18
20
22
24
26
0
2
4
6
8
12
17
22
26
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

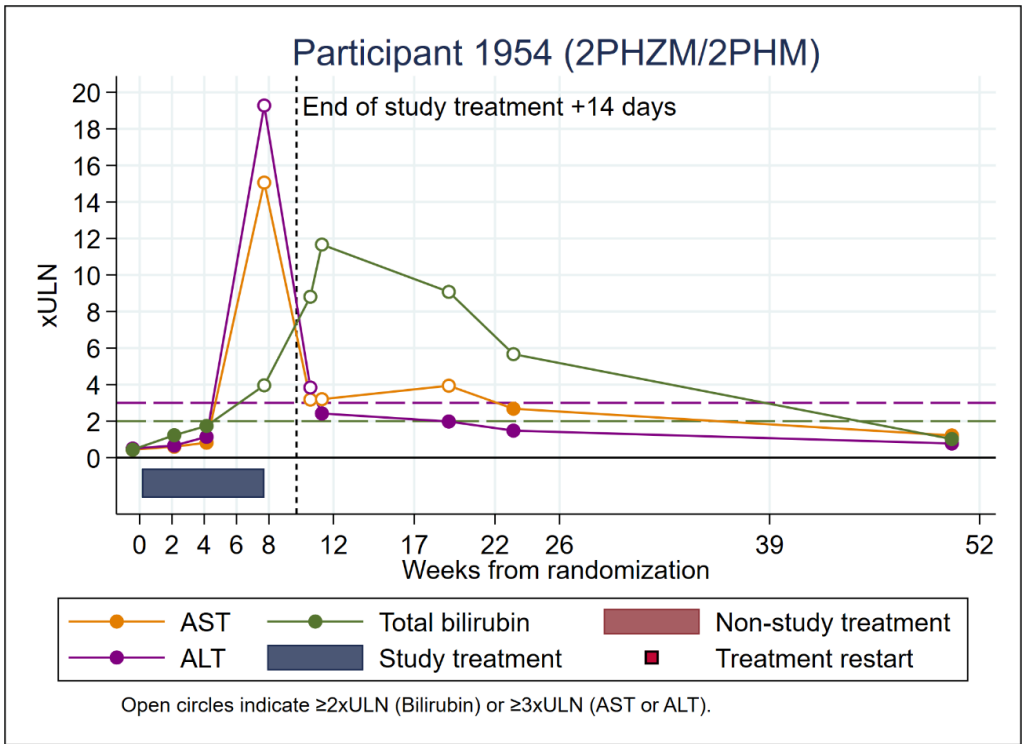

Participant 1249 (2PHZM/2PHM)
End of study treatment +14 days
xULN
10
9
8
7
6
5
4
3
2
1
0
0
2
4
6
8
12
17
22
26
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

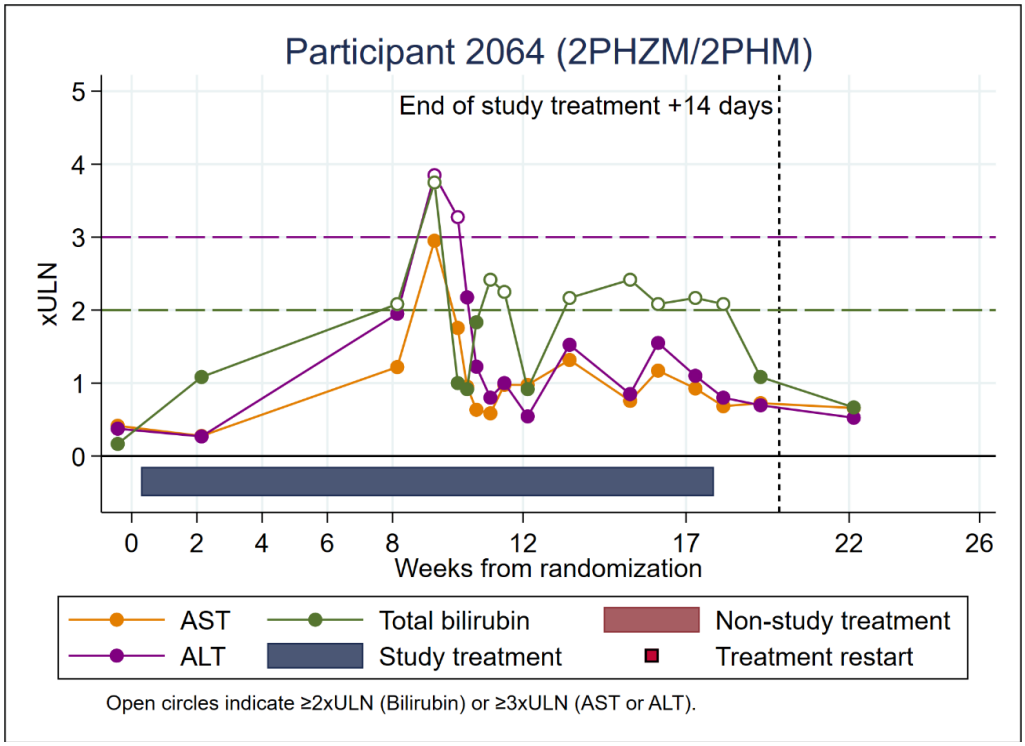

Participant 1527 (2PHZM/2PHM)
End of study treatment +14 days
xULN
5
4
3
2
1
0
0
2
4
6
8
12
17
22
26
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

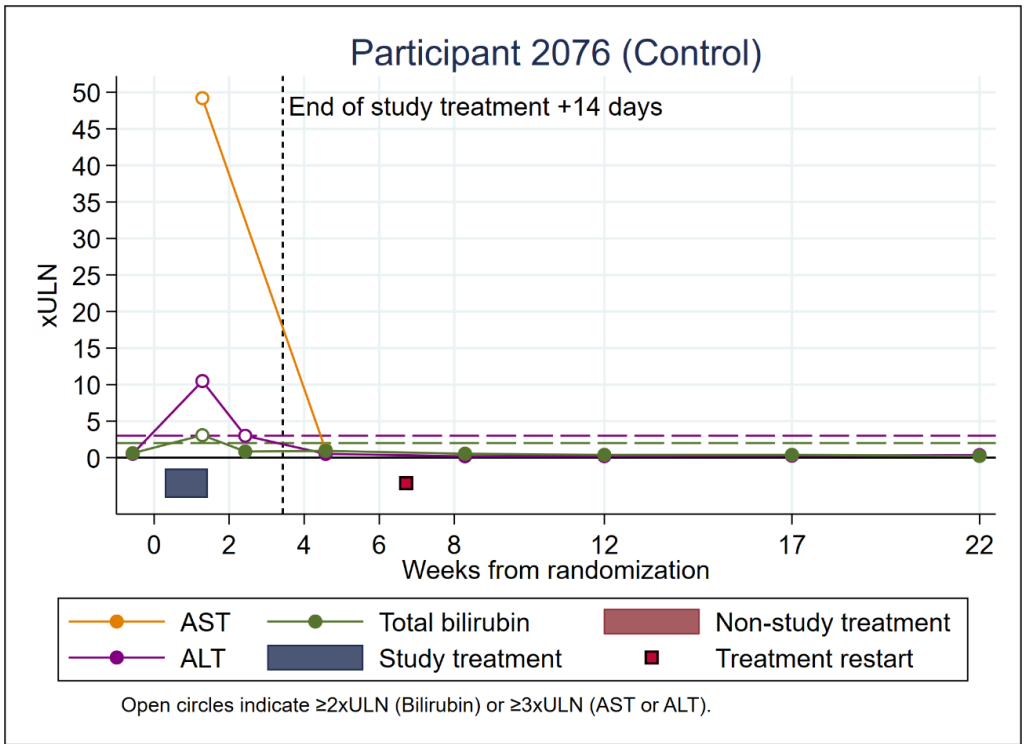

Participant 1528 (2PHZE/2PH)
End of study treatment +14 days
xULN
0
1
2
3
4
5
6
7
8
9
10
0
2
4
6
8
12
17
22
26
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

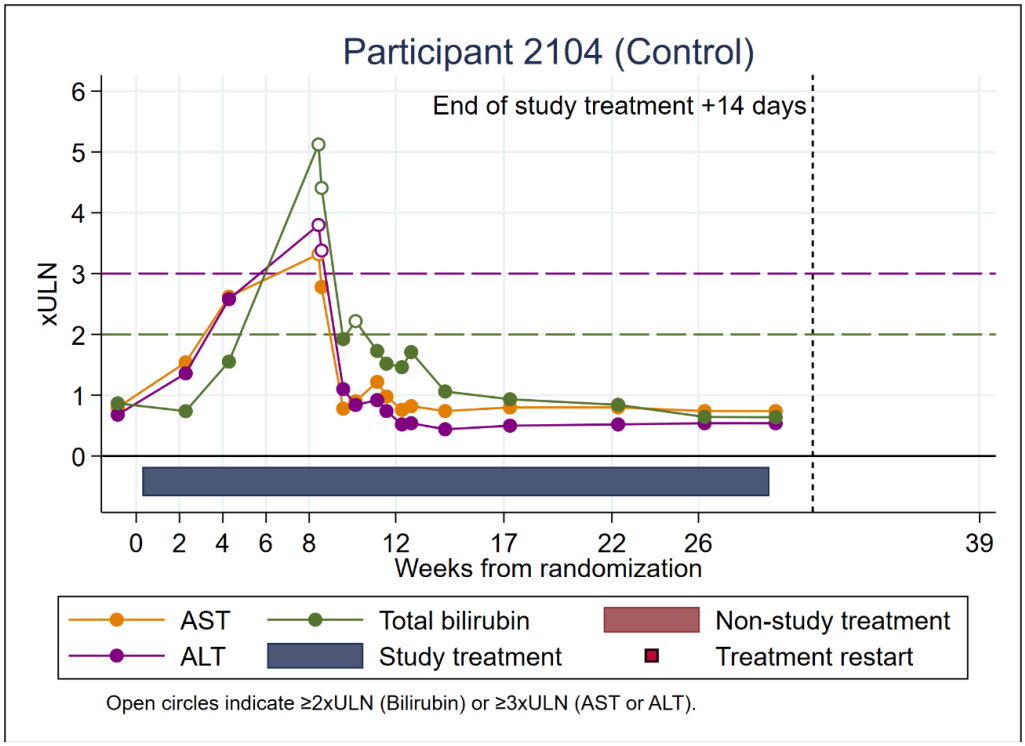

Participant 1699 (2PHZE/2PH)
End of study treatment +14 days
xULN
0
2
4
6
8
10
12
14
0
2
4
6
8
12
17
22
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

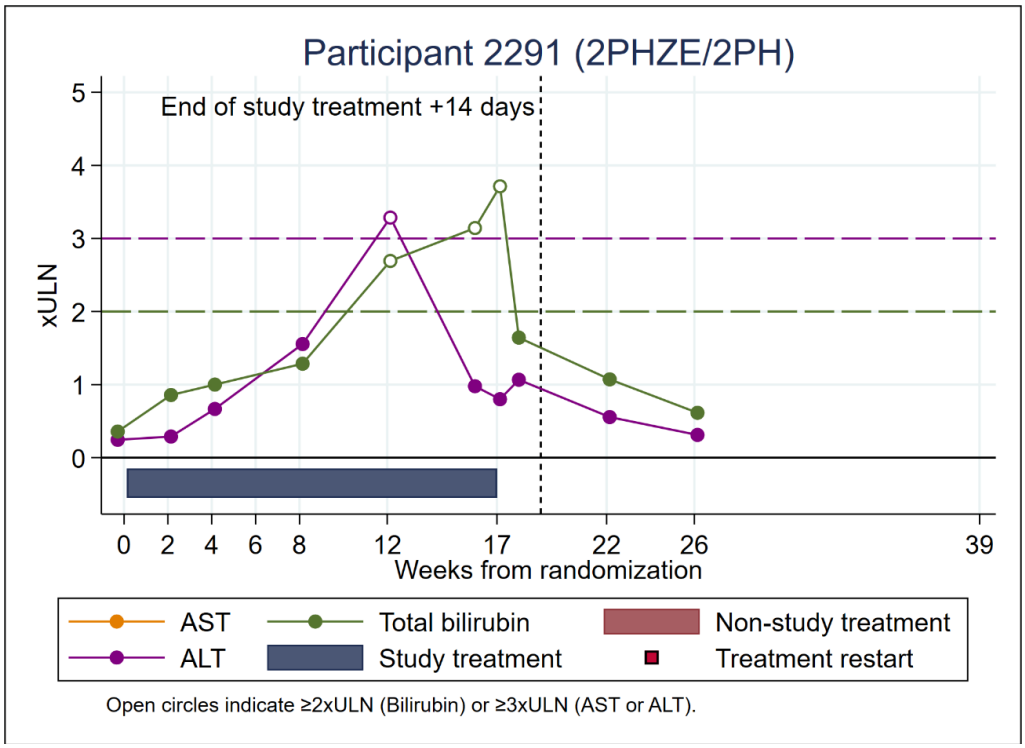

Participant 1871 (2PHZM/2PHM)
End of study treatment +14 days
xULN
0
1
2
3
4
5
6
0 2 4 6 8 12 17 22 26
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

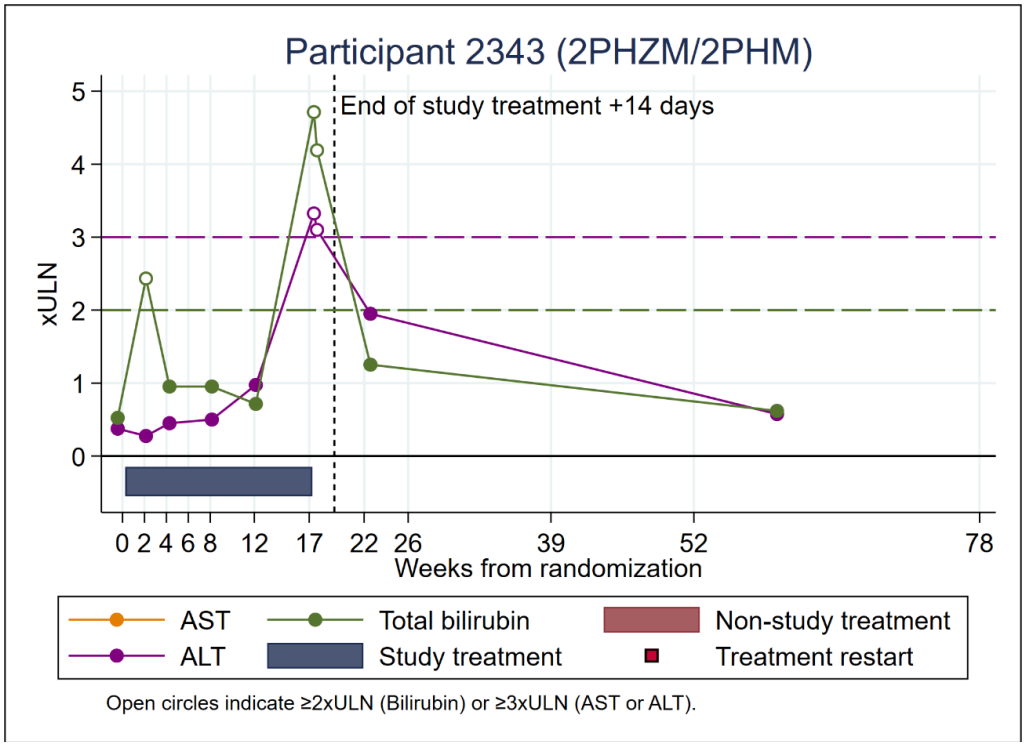

Participant 1954 (2PHZM/2PHM)
End of study treatment +14 days
xULN
0
2
4
6
8
10
12
14
16
18
20
0 2 4 6 8 12 17 22 26 39 52
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

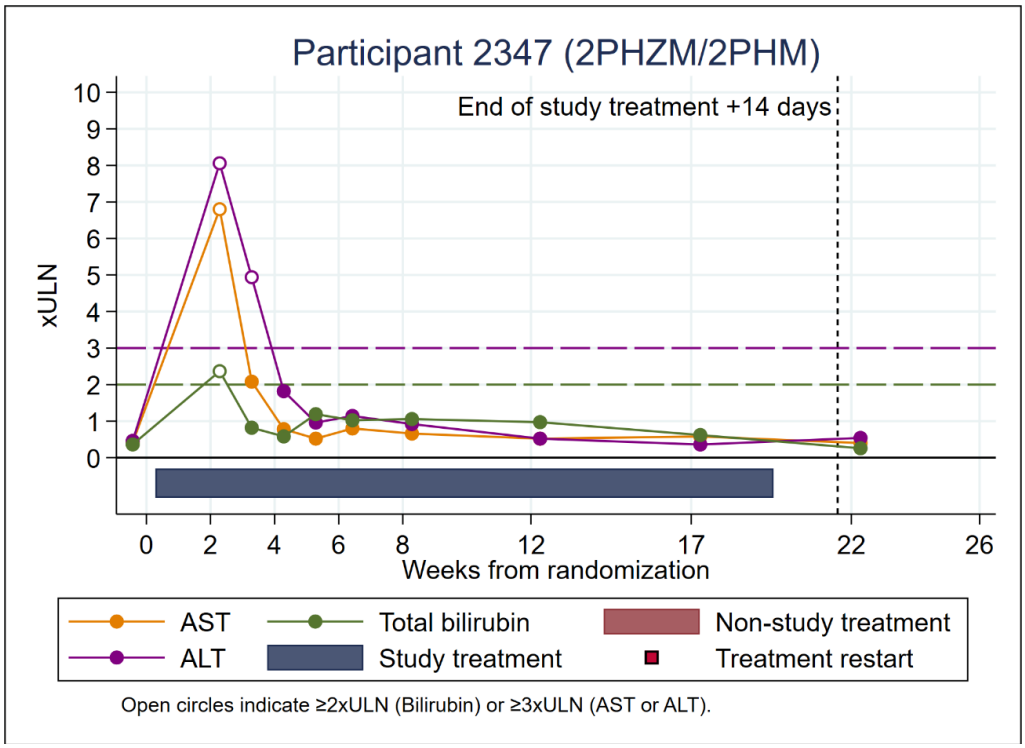

Participant 2064 (2PHZM/2PHM)
End of study treatment +14 days
xULN
0
1
2
3
4
5
0
2
4
6
8
12
17
22
26
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).


Participant 2076 (Control)
End of study treatment +14 days
xULN
0
5
10
15
20
25
30
35
40
45
50
0
2
4
6
8
12
17
22
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).


Participant 2104 (Control)
End of study treatment +14 days
xULN
0
1
2
3
4
5
6
0 2 4 6 8 12 17 22 26 39
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).


Participant 2291 (2PHZE/2PH)
End of study treatment +14 days
xULN
0
1
2
3
4
5
0 2 4 6 8 12 17 22 26 39
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).


Participant 2343 (2PHZM/2PHM)
End of study treatment +14 days
xULN
0
1
2
3
4
5
0 2 4 6 8 12 17 22 26 39 52 78
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).


Participant 2347 (2PHZM/2PHM)
End of study treatment +14 days
xULN
0
1
2
3
4
5
6
7
8
9
10
0 2 4 6 8 12 17 22 26
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

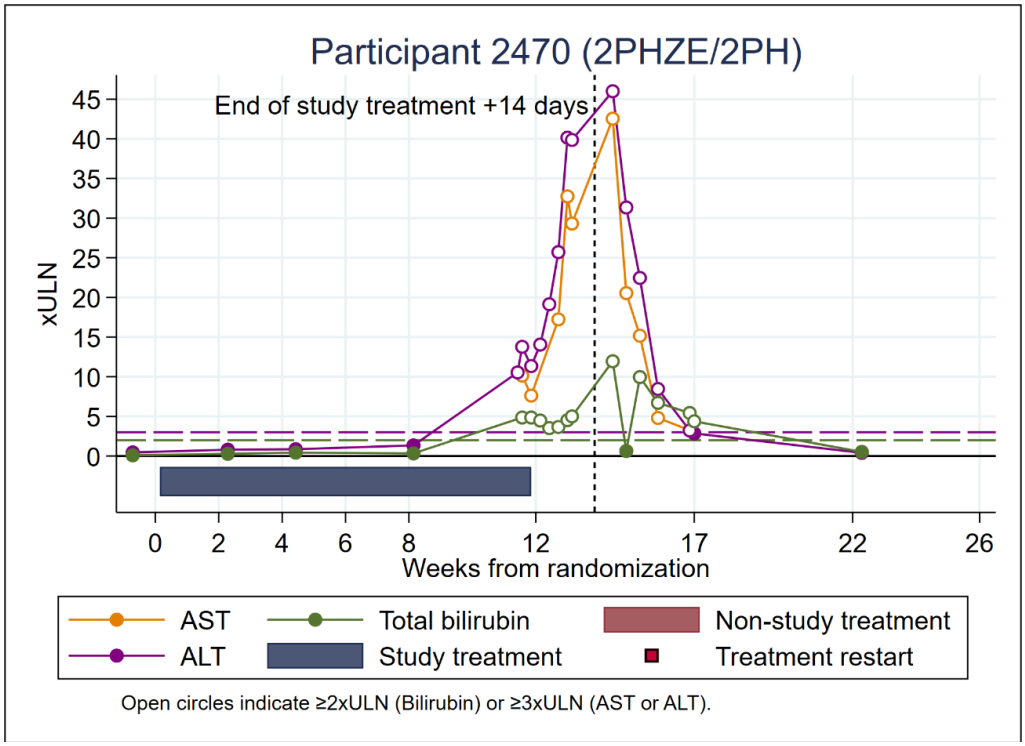

Participant 2470 (2PHZE/2PH)
End of study treatment +14 days
xULN
45
40
35
30
25
20
15
10
5
0
0
2
4
6
8
12
17
22
26
Weeks from randomization
AST
ALT
Total bilirubin
Study treatment
Non-study treatment
Treatment restart
Open circles indicate ≥2xULN (Bilirubin) or ≥3xULN (AST or ALT).

Table S16. Table: Study 31/ACTG 5349 Key Elements of Mycobacteriology Laboratory Procedures.

	Laboratory Procedure	Key Element in Procedure	Potential Affect/Impact
1	Sputum Collection & Transport	Participant is to rinse mouth with boiled/sterile/bottled or distilled water prior to sputum collection	Quality of specimen
2	Sputum Collection & Transport	Collect at least 3 to 5 mL of sputum. If larger volumes cannot be obtained, a minimum of 1 mL is acceptable[i]	Quality of specimen
3	Sputum Collection & Transport	Transport sputum specimen to the laboratory in a cool box as soon as possible after collection. Store sputum in a refrigerator or cool box (2-8°C) if not received by to the laboratory within 1 hour of collection[ii]	Integrity of specimen
4	Sputum Receipt & Storage	Store sputum specimen in a refrigerator or cool box (2-8 °C) if not processed within 1 hour of receipt at the laboratory	Integrity of specimen
5	Sputum Processing	Decontaminate sputum specimen with a final sodium hydroxide (NaOH) concentration of 1.0 to 1.5% for 15 to 20 minutes prior to adding phosphate buffered saline (PBS) (pH 6.8)	Isolation of MTB
6	Sputum Processing	Centrifuge specimen with a relative centrifugal force (RCF) of 3000x*g*, for at least 15 minutes[iii]	Isolation of MTB
7	Sputum Processing	Resuspend the digested decontaminated specimen to final volume of 1.5 to 2.0 mL with PBS (pH 6.8)[iv]	Comparability of results
8	Sputum Processing	Include positive controls at least once per week or with each participant batch, and negative controls daily or with each participant batch	Isolation of MTB and Detect Cross-Contamination
9	Smear Microscopy	Positive and negative control slides must be included with every batch of participant slides	Quality of smear results
10	Smear Microscopy	Report results according to WHO/IUATLD grading scale as per the Global Laboratory Initiative (StopTB Partnership) Sputum Microscopy Handbook[v]	Comparability of results
11	Rapid Molecular Testing	Perform rapid molecular test (e.g., GeneXpert) according to the manufacturer's product insert	Comparability of results

	Laboratory Procedure	Key Element in Procedure	Potential Affect/Impact
12	Rapid Molecular Testing and Smear Microscopy	Report results of screening tests used for subject eligibility to clinic staff within 48 to 72 h of sputum specimen receipt	Turnaround time
13	Solid Media Culture	Inoculate solid media (slant or plate) with 0.2 mL of resuspended sputum sediment[vi]	Comparability of results
14	Solid Media Culture	Incubate solid media for at least 6 weeks before reporting a negative result; or at least 8 weeks for drug resistant TB trials	Isolation of MTB
15	Solid Media Culture	Test appropriate controls before media is used, regardless if purchased commercially or prepared in-house[vii]	Isolation of MTB
16	MGIT Culture	Inoculate each MGIT tube with 0.5 mL of the resuspended sputum sediment	Comparability of results
17	MGIT Culture	Work up all MGIT cultures (positive and negative) according to the FIND MGIT Manual and MGIT culture algorithms/flow charts included in the study-specific laboratory reference manual[viii]	Isolation/Detection of MTB
18	Identification of MTB	Confirm the presence of *M. tuberculosis* complex (MTBC) vs. non-MTBC at each trial time point when culture is positive[ix]	Isolation of MTB
19	Identification of MTB	Include positive and negative controls at least once per week or with each batch of participant specimens and with each new lot or shipment of testing kits/reagents	Accuracy of MTB ID
20	Drug Susceptibility Testing (DST)	Include a drug susceptible quality control (QC) strain at least once per week or with each batch of participant specimens	Quality of DST results

[i] If not possible to collect at least 1 mL expectorate sputum, use local procedures for sputum induction, when necessary

[ii] When the distance between the clinic and laboratory is great (i.e., the clinic ships the specimen to a regional laboratory), the specimen should be maintained on cold chain and received at the laboratory no more than three to five days after collection.

[iii] Use of a refrigerated centrifuge is preferred.

[iv] For guidance on how to achieve accurate and precise resuspension volumes, please see Study 31/ACTG 5349 Mycobacteriology Laboratory Reference Manual.

[v] See Section 9, "Acid-fast Bacilli Microscopy (AFB) Examination", from Global Laboratory Initiative Stop TB Partnership. Laboratory Diagnosis of Tuberculosis by Sputum Microscopy – The Handbook

2013. Available from: http://www.stoptb.org/wg/gli/assets/documents/TBLabDiagnosisSputum%20Microscopy_Handbook.pdf.

[vi] If using slants or plates where 0.2 mL of inoculum would overwhelm the surface area of the media, inoculate additional slants or plates so that the total volume of resuspended sputum sediment cultured on solid media is 0.2 mL. See Study 31/ACTG 5349 Mycobacteriology Laboratory Reference Manual.

[vii] See Section 16, "Quality Assurance", from Global Laboratory Initiative Stop TB Partnership: Mycobacteriology Laboratory Manual. First edition, April 2014. Available from: http://www.stoptb.org/wg/gli/assets/documents/gli_mycobacteriology_lab_manual_web.pdf

[viii] See Study 31/ACTG 5349 Mycobacteriology Laboratory Reference Manual.

[ix] At least one positive culture (e.g., AFB-positive MGIT) at each time point for each participant should be identified as *M. tuberculosis* or otherwise, depending on the laboratory resources. See Study 31/ACTG 5349 Mycobacteriology Laboratory Reference Manual.